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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

HOWARD REID CRAIG

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Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation 5:201 (Feb.) 1952.

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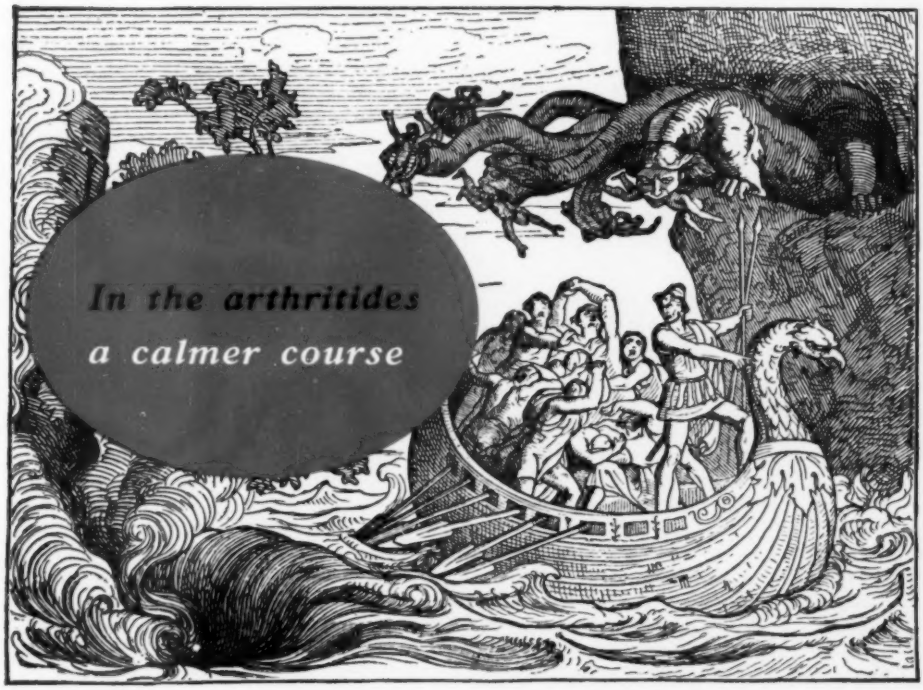

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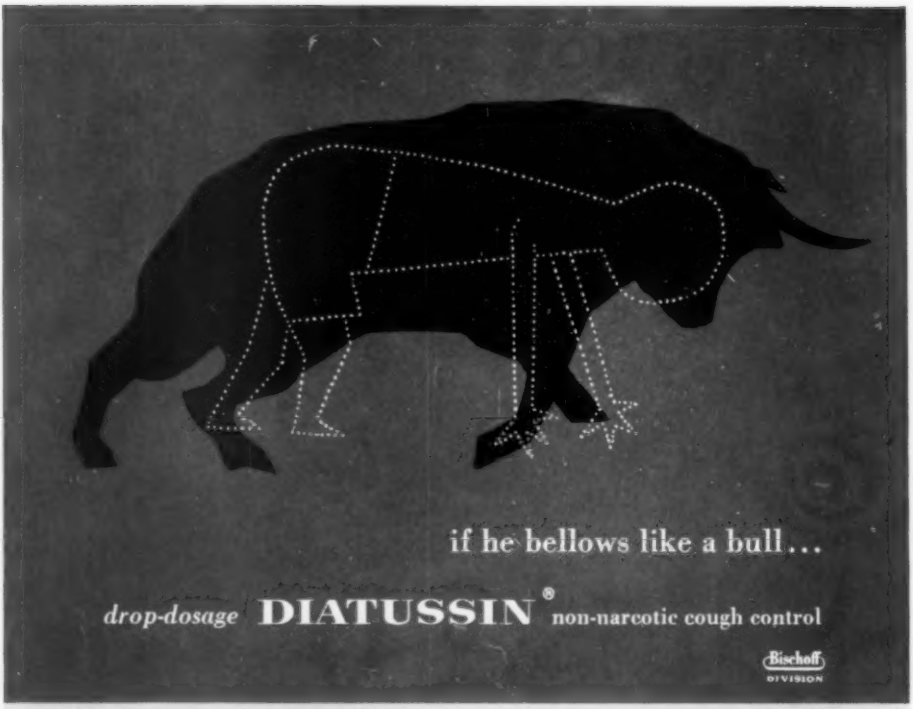

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 32, NO. 10 OCTOBER 1956

THE NEW YORK ACADEMY OF MEDICINE: RETROSPECT AND PROSPECT*

HOWARD REID CRAIG

Director, The New York Academy of Medicine

EDUCATIONAL institutions are the product of the times in which they are born and in general reflect an attempt to answer some current pressing need. Their success and survival have depended on the effectiveness with which they have been organized to meet that need and the ability and flexibility with which they have adapted themselves to the changing needs and conditions of changing times. We see this illustrated in almost every walk of life. In our own time we have seen banking become in large part a real estate, trust and investing agency. The Church has become almost more an agent of social service than of creed, dialectics or apologetics. The profession of law in dollar volume of business partakes more of the problems of corporations and taxation than of the personal services out of which law and justice originally grew. Even the automobile industry now produces refrigerators, washing machines and Diesel engines, and the commercial chemists are in the textile business; and so it goes. The ability to recognize and appraise

* Presented before the Committee on Medical Information, May 14, 1956 and before the Committee on Public Health, June 4, 1956.

changing conditions and oncoming needs and the capacity to meet these alterations of environment will largely determine the survival and the effectiveness of any organized group, industrial or educational.

It is, however, not enough merely to recognize problems and changes in their incipiency. Wisdom and the full knowledge necessary to solve present day problems require a sound understanding and an objective evaluation of the past which is the parent of today. Winston Churchill has written, "Knowledge of the trials and struggles [of the past] is necessary to all who would comprehend the problems, perils, challenges and opportunities which confront us today."

It therefore behooves us, as Fellows of this Academy, to take a glance backward and try to cull from the history of the Academy some of the salient influences and events that have shaped its course and have determined its present form and functions. The Academy, back in 1847, did not spring full blown from a vacuum,—with full apologies to Minerva and Zeus for a possibly well mixed metaphor. Rather it was the child of perilous times in American medicine. It must have taken more than an urge for social intercourse to bring together a hundred and eighty practicing and teaching physicians with the intent of setting up a permanent organization. Quackery of innumerable varieties flourished like the green bay tree and even legitimate medicine, if one may use this questionable designation, boasted of no clear definition, as perhaps it never has and it is hoped never will. In 1847 medical education as we know it today was not. Nor for thirty years was there an established organized university medical curriculum in this country. Provisions for qualification and licensure were confused and unclear. The times cried out for some coordination and organization of medical education and some standardization of the level of medical practice. Clinical research was notable for its absence though this fact is understandable in a nation which, though only seventy years old, had been engaged in four separate wars. Scientific intercourse with the medical centers of Europe amounted to very little and the medical literature emanating from Europe was slow in crossing the Atlantic, variable in quality and hard to come by.

Churchill's remark that the English people were without hot baths and central heating for over 1500 years, from 400 A.D. to the end of the Nineteenth Century, may well have applied on this side of the Atlantic. Dirt, squalor, impure water, epidemic infection, lack of

adequate sewage disposal, all characterized New York City in the eighteen-forties. Sanitary measures were spurned and distrusted. Even the introduction of the inside water closet was distrusted and rejected by some of our leading practitioners, one of whom, a leading obstetrician of the time, removed his parturient wife from the malignant effluvia and miasmata of the inside water closets of New York City to Nyack, New York, where the old-fashioned outhouse and the clear air of Rockland County would prevent possible puerperal sepsis.

No wonder then, that, under the pressure of the times, thinking men, motivated by high ideals, banded together to form an Academy in order to improve medical education and practice which sorely needed improvement; to establish a common library to make available the current medical literature and lastly, to encourage those measures which would improve the public health.

Let us recognize at the outset that the Academy was formed to meet needs and demands which faced the medical profession and the community as a whole. It was a product of the times, not an incidental sport. This fact may well account for its survival over the ensuing decades through internal storms and external stresses. I do not propose to tax you with a detailed history of the Academy; the facts in chronological order may be found in Van Ingen's history. I would rather direct your attention to some of those events which have had a direct bearing on the position and responsibilities of the Academy today. Suffice it to say that the Academy had a direct hand in establishing the New York City Department of Health and that its Fellows and its officers were among the leaders in the development of the local medical schools. The Library, initially housed in the office of one of the Fellows, grew, mainly through personal gifts and benefactions and through the leadership and generosity of Dr. S. S. Purple until, housed in the Academy's own building on West 31st Street, it assumed the proportions of a real reference library. The erection of the new building on 43rd Street in 1890 began a notable epoch for the Academy, characterized chiefly by library growth and expansion. Fundamentally, however, the institution was in character an atheneum—a pleasant place to read or study or perhaps to doze, with occasional meetings to wake the somnolent,—meetings characterized ofttimes more by the heat of the discussions than by the cold logic of the views expressed.

With the turn of the century and particularly in the second decade

of the Twentieth Century, a new influence was brought to bear on the Academy. Increasing concern for the health of the general public, renewed interest in the relationship of government and its agencies to health and the costs thereof, speculations as to the effectiveness of hospital and dispensary care, the publication of the famous Bulletin No. IV by the Carnegie Corporation,—the so-called Flexner report,—all these and other comparable phenomena became matters of public interest and it was to the Academy that that public turned. From this demand was born the first of our present standing committees, that on Public Health. Thus we see again that a major turn in the affairs of the Academy was the result of a trend in the thinking of the times. From that time on, the Academy has played a major part in most of the movements for better public health for the city, the state and the nation. May I quote from a letter of the past month to the Executive Secretary of the Committee on Public Health from the present Commissioner of Health of this city, "I do hope you and the Committee realize how much we appreciate the many hours of labor that go into the preparation of documents like these. I don't know how this department could function effectively without the continuing criticism, wisdom and advice of the Committee on Public Health of The New York Academy of Medicine. I am afraid we don't say thank you very often. This seems to be a particularly appropriate time to do so." The strength of this Committee has lain in the objectiveness, the enthusiasm and breadth of view of its members, its Chairmen over the years, Drs. Dana, Miller, Baehr, Mustard, Bailey,—and its Executive Secretaries, Drs. Corwin and Kruse and their staffs, whose effectiveness, competence, diligence and loyalty are well known to all of the Fellows of the Academy.

The years from 1923 on were exciting ones. Through the munificence of the Carnegie Corporation, plans were made for our present building. The Rockefeller Foundation made a grant of a million and a quarter dollars toward endowment. A full time Director, in the person of Dr. Linsley R. Williams, was installed and the Academy began to assume a real and important role in the life of the community.

There had been in existence for a number of years, the Society for Clinical Information and the New York Association for Medical Education. The increasing importance of New York and the United States as a whole as a medical Mecca, drew hundreds of foreign physicians to New York seeking additional knowledge and training. To meet

these and other demands in the field of medical education, the associations cited above merged to form a standing committee of the Academy, that of Medical Education, with a full time Executive Secretary. At the same time publication of the Bulletin, which had previously appeared only sporadically, was resumed. Both of these projects were originally underwritten by grants from the Rockefeller Foundation, but since that time have been strengthened and carried on solely as part of the Academy's own responsibility. Here again we see a standing committee of today initiated in response to a pressing professional need, a need which is even more urgent today than in the days of its beginnings. Problems of extra-university education, problems of internships and residencies, of foreign physicians, of hospital-practitioner relationships, all these and many more are the business of this committee. It provides a common meeting ground for medical education at all levels for exploration and cooperation.

The genesis of the Committee on Medical Information is an interesting one. Originally started in 1928 as a joint venture of the Academy and the New York County Medical Society, dubbed the Medical Information Bureau, it purposed "to facilitate the dissemination of authentic information on medical and public health matters; to stem and curtail quackery [cf. 1847!] and to promote better understanding between the public and organized medicine." Again we see an agency set up to meet an urgent need. I do not have to recount to this group the multiplicity and diversity of the activities and products of this Committee, news releases, radio broadcasts, news articles, magazine articles, information services, laity lectures, conferences on many subjects. It is interesting to note that despite the broad field in which this Bureau operated, it did not become a standing committee of the Academy until 1938. Aside from the demanding and taxing duties inherent in the original purposes of the Bureau, the dramatic aspect of the work of this Committee has been its absorption with problems which lie on the periphery of what is thought of as pure medicine, its attempts to explore those outer limits where the so-called science of medicine merges into other professions, other disciplines, where it impinges upon or, better still, becomes thoroughly integrated into the problems of the communal life of our present social economy. The report on Medicine and the Changing Order was conceived in this committee. The important conferences for health workers, that on the

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relationship of ministry and medicine, on panic and morale, all bear witness to the sensitivity of this committee to what is transpiring in this changing world of today. The strength of the committee is the strength and enthusiasm of its members, its Chairmen over the years, Moorehead, Kopetzky, Mixsell, Armstrong, McGowan, Peightal, Master,—and its Executive Secretary with his able staff.

I have tried to show through this sketchy story of the Academy and particularly its functioning committees that every major progressive step in its unfolding has been an attempt to meet some urgent problem of the time. The picture is somewhat analogous to the situation which Clinton Rossiter discusses in his recent book, "The American Presidency." He cites Jackson, Lincoln, the two Roosevelts and Wilson as men who have dramatized the institution of the Presidency. He goes on to picture Mr. Eisenhower as acting in the tradition of strong Presidents, not so much by design or plan or the inherencies of the Constitution, but by reason of "meteorological changes in the climate of politics and customs." The medical and social climate in which the Academy was born, was reared and matured determined its present functions and its present place in the community.

Where and how do we stand today? Having acquired some insight into how we got here, the next step is to appraise our present organization. The accompanying chart shows graphically the present scheme of organization of the Academy. The Council, which is made up of the Officers, Trustees and the Chairmen of the five Standing Committees, is the governing body of the Academy. All of these men are Fellows of the Academy, are therefore physicians, and are elected by the Fellowship, except the Chairmen of the Committees on Medical Education, Public Health and Medical Information who are elected by their respective Committees, the members of which are appointed annually by the President. The Council is responsible for all matters of general policy affecting the Academy as a whole. The Board of Trustees, in addition to sitting as part of the Council, is specifically charged with setting up the annual budget, directing the disposition of Academy assets including its invested funds, and the management of the building and other real estate holdings. The responsibility for overall administration rests with the Director who is answerable directly to the Council and who, together with his executive staff, namely, the Comptroller, the Librarian, and the Executive Secretaries of the Com-

mittees on Medical Education, Public Health and Medical Information, carry on the day to day activities of the Academy. Each of these Executives has his own working staff. The Academy today employs one hundred and fifteen persons, of whom about fifty form the Library staff.

The Academy Fellowship is divided into twelve Sections, according to specialties or interests, each of which meet approximately monthly. These Sections set up their own programs and general policies, subject to the approval of the Council, and elect their own Chairmen and Secretaries. These Officers, two from each Section, constitute the Committee on Sections under the Chairmanship of one of the Vice Presidents of the Academy.

The Committee on Admission, an elected Committee, screens and passes on nominations for Fellowship which are then voted upon by the Fellowship as a whole at Stated Meetings.

In brief, this is the present operational organization of the Academy. It is obvious that it involves the cooperation, real interest and team work of several hundred individuals without reference to the help and constructive ideas of many other Fellows who do not, at a given moment, hold office or committee membership.

The next question to ask of ourselves is, "How do we stand financially?" To quote Churchill again, "The power of any government depends ultimately upon its finances." Truer word was never spoken. At the present time, the total assets of the Academy amount to something over seventeen million dollars, at the present market. Of this amount, $5,779,831 may be classed as fixed assets, that is, land and buildings at $2,537,481, furnishings and equipment at $252,350, and Library holdings by a recent appraisal at $2,990,000. Cash and investments amount to $7,000,000 at cost and at the present market about $12,000,000, of which approximately 70 per cent are in equities. So much for assets.

Now how about operation? I have prepared figures showing budgets and operating figures back to 1939, a period of seventeen years. With these I am not going to burden you, but it is of some interest that the total operational budget for the year 1939 was $256,280 of which the Library received $89,352. The budget for 1956 calls for expenditures of $617,802, of which the Library will receive $250,802. It may be of interest to you to know how the balance of the $617,802 in this year's budget will be spent. Overall administration will cost $149,019,

building operation $86,226, Medical Education $51,775, Medical Information $38,039, and Public Health $41,941.

You may now ask where does this money come from? First, from interest and dividends on investments, $356,000 approximately; from dues $110,000; Library fees, $7,000; room assessments $41,000; the Academy Bulletin $38,000; contributions $54,000; photostats $26,000; bibliographic services, $6,000; miscellaneous (Fortnight, etc.) $4,000. These are round figures drawn to the nearest thousand.

I have given you these figures, not to bore you, but to impress on you the fact that, businesswise, the Academy of Medicine is not an infant in swaddling clothes; and also to bear witness as eloquently as I can to the wisdom, the diligence and the conscientiousness which the Trustees of the Academy apply to the responsibilities and the trust which they have assumed. I have studiously avoided mentioning names in this talk, but I cannot pass on without paying tribute to each member of the Board of Trustees: Orrin Wightman, Chairman; Shepard Krech, Treasurer and Chairman of the Finance Committee, and Committee members Harold Mixsell, George Baehr and Condict Cutler; the Committee on Budget, Bradley Coley, Barclay Parsons and Henry Riley and the Committee on Building and Property, B. P. Watson, Asa Lincoln and William MacFee. The financial level at which the Academy operates today is only possible through wise and judicious handling of its resources, by economical administration in the face of rising costs and the wholehearted cooperation of the Fellowship as a body and the staff of the Academy in particular. I think it is only appropriate that I take the opportunity at this point to express my own deep gratitude for the help, cooperation and understanding that I have received without exception from the succeeding Presidents of the Academy, the Trustees and Council, the members of the committees, the Fellowship as a whole, and the loyal hardworking staff of which the Academy may be justly proud. Next October first it will be ten years since I assumed the Directorship, the longest tenure since Linsley Williams. Despite the fact that I thoroughly enjoyed practice and hospital work and teaching, these have been my happiest and most satisfying years.

Now what of the future? First, let us be fully aware that as Fellows of the Academy we are participating members of an institution rich in tradition, strengthened by a record of over one hundred years of service to the profession and to the community and manned by the best

medical brains in the city or, for that matter, in the country. Emphasized as well should be the fact that this Academy is under no direct obligation to any individual or to any group of individuals outside its own roster. This freedom of action within the limits of wisdom and good judgment has made it possible for the Academy to pioneer in many fields which have been verboten to other groups. Some of these efforts have been futile and fruitless, but many others have blazed trails which others more circumscribed or less courageous have followed, witness the Maternal Mortality report, the Medicine and the Changing Order report, the Perinatal Mortality report, the recommendations as to narcotic control, the reports on the use and misuse of barbiturates and on the transmission of viral hepatitis, the latter two of which will appear in current issues of the Academy Bulletin,—all of these and many others too numerous to enumerate. Accomplishments like those mentioned, to say nothing of its intramural medical educational programs, have established the Academy's national reputation for thorough soundness, lack of bias and complete absence of self interest. There is no other group in this country comparable to it. Lambert in 1927, quoted by Goodridge in 1941, wrote: "The New York Academy of Medicine is not a local group. It has become a national institution. This Academy like every educational institution must go on to new fields of work or retrograde and slip from its position of prominence." Possibly trite, but nevertheless wholly true. The greater the position, the greater the responsibility.

We are living in times of rapid change. New concepts, new tools, new attitudes in medicine and in the world at large take form almost by the hour. What was useful and needful a few decades ago is today forgotten. What we accept today as commonplace was undreamt of a few short years back. The Academy, in some aspects, at least it seems to me, is operating to a degree in the framework of twenty-five years ago. The Library has kept apace and even led in the library world, but it works in an altered climate. The growth of the university medical libraries has been a great factor in decreasing the reader census in our library halls. It may be of interest to you that less than fifty per cent of the readers in the library are doctors and of those, only about twelve per cent are Fellows of the Academy. The remainder come from industry, from the lay press, free lance journalism, the entertainment world and lay scholars. On the other hand, the auxiliary services such

as current reference services, microfilming, Cormack reproducing, etc., have increased. Staff turnover in the lower grades is rapid as it is throughout industry in times of high employment. However, it is my conviction that regardless of demand or operational problems or costs or competition, the Library, as our greatest material heritage and treasure, must be maintained at full strength and full effectiveness.

The future for the Public Health Committee, in terms of opportunity and challenge, is a happy one. At no time in history has the public health movement and the general concern for the health of all the people reached a higher point. Here again has occurred a change in attitude and approach. The intense focus on sanitation and infection of the years past has veered toward the prevention of disabling degenerative diseases, nutrition and the field of mental health. Preventive medicine and public health are approaching closer and closer to medical practice. With proper understanding, and *only* through a full bilateral understanding, the eventual marriage of these two interests will prove a successful and beneficial one. These new trends have put added burdens on our Public Health Committee which have taxed its resources but which to date have been met with sagacity, good judgment and a proper sense of proportion and values.

I am not going to dilate on the problems of our Committee on Medical Education. They are of two orders: internal—such as diminished attendance at local meetings, the plethora of meetings in general, the difficulty in setting up programs that are not a rehash and whose speakers are not the same authorities speaking again and again. There just is not enough new worth while material to justify the number of meetings held all over the country. Of external problems, the Committee is actively participating in the study of the intern and residency question, the education and licensure of foreign physicians and experiments in medical school curricula which badly need overhauling. This, I feel, is one committee which with the passage of time needs re-orientation and a possible change of direction.

As we saw earlier, the Medical Information Bureau initially had almost entirely to do with the press and lay publications. As we know, its field of operation has broadened tremendously. It has been said again and again that medicine has become almost as much a social science as a biological science. Medicine is not a thing apart; it is an integral portion of the warp and woof of human existence. Its relation to how

people live, why they behave as they do, how they have come to be as they are, what are their beliefs, has received fairly general acceptance only in the recent past. All of this connotes a closer community of interest between all the professions and the disciplines to which our present civilization is heir. Only recently I heard an able Judge of our Supreme Court ask in full sincerity, "To what degree is our State Supreme Court a social agency and conversely to what extent is it merely a cold mechanism of justice?" A healthy and suggestive question.

There are changes in our times which merit study and examination. Medicine in our time has become a complicated and diverse entity, if it is an entity. Industry, unions, insurance, education, public health, legislation, to say nothing of the confusing economics surrounding the practitioner, all are marching onward to God knows where. I propose no blueprint for this Academy, but the fields are there to be cleared, ploughed and harrowed. Only then can they be seeded and some harvest anticipated. The proposed "Whither Medicine" exploration is a first step in the right direction. The Academy is unfettered. It is not limited to medical education, to public health in the accepted sense or to the academic or the traditional. That to me is the responsibility, the challenge and the opportunity of this Academy.

A future for the Academy should be based on three major components which should never be forgotten or lost sight of. The first of these is service. Whether that service be to the Fellows themselves, to the medical profession at large, to other agencies or to the non-medical community at large,—whether that service be personal or in terms of the various committees or the Library, makes not one whit of difference. Service is the rock on which the Academy has been built and stood firm over the years. The second component is a spirit of inquiry, a willingness to explore and pioneer and experiment, whether it be in the area of traditionally accepted tenets or whether it be in the vague hinterland of our present understanding. Tangible material results are not as important as the spirit which is willing to hazard a foray into unknown territory. And finally, may the Academy always maintain a detached, critical and objective attitude toward the problems that it faces, rejecting the false and recognizing the true. May it always heed the admonition of St. Paul to the Thessalonians to "Prove all things [and] hold fast to that which is good."

NEUROSURGICAL ALLEVIATION OF PARKINSONISM*

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I AM very grateful for the invitation to take part in this Graduate Fortnight which is concerned with the problem of geriatrics and chronic diseases. The Committee has asked me to review briefly the current status of the neurosurgical therapy of parkinsonism and to demonstrate and comment upon the results which have been achieved in our own investigation into this problem. These remarks supplement the technical exhibit on neurosurgical therapy of parkinsonism which has been on display during the Fortnight.

Since 1817 when James Parkinson described the syndrome of the shaking palsy which bears his name, there has been a sustained interest in developing new methods of therapy for this affliction. This interest has thus far resulted in little concrete progress toward the development of a specific medicinal agent which will either eliminate the disabling symptoms of parkinsonism or halt its inexorable course once the first sign of shaking palsy has made its appearance. Thus, in our present state of knowledge the progress of parkinsonian tremor and rigidity and gait abnormalities, as well as the other stigmata of parkinsonism, is usually relentless and inevitable. The average patient will usually reach a lingering stage of almost total helplessness; speechless, expressionless, unable to move at will but constantly shaking from involuntary tremor, and held in a prison of his own rigid musculature.

It is this invariably pessimistic prognosis that has led some patients to submit to brain surgery in the hope of a degree of alleviation from their symptoms, and has led some neurosurgeons to attempt procedures for such alleviation. It is the purpose of this discussion tonight to review briefly the procedures which have been attempted by neurosurgeons up to the present time and to describe specifically two original tech-

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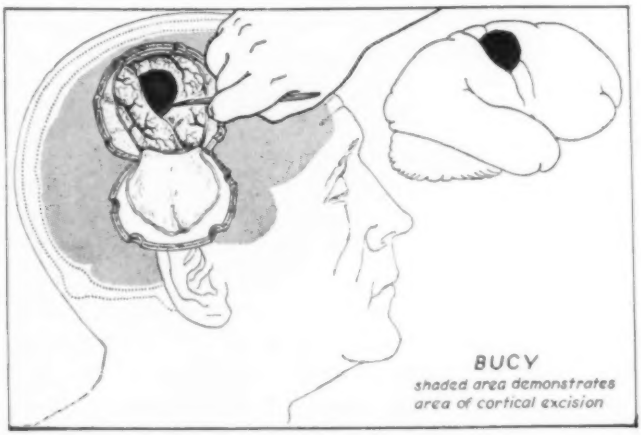

Fig. 1.—Demonstration of Bucy's cortical excision operation for parkinsonian tremor. This procedure results in contralateral hemiplegia or hemiparesis with resultant lessening or abolition of tremor.

niques which have been employed in a series of 145 cases, on our own service. It is my opinion that neurosurgical therapy has reached a stage where it may be considered a reasonably safe, practical, and useful tool for the treatment of many cases of parkinsonism. I should like to present some of the results of such treatment during the course of this presentation tonight.

Review of Neurosurgical Approaches to Parkinsonism

The Pyramidal Tract Operations: During the past two decades, neurosurgeons have devised operations at virtually every level of the nervous system during their attempts to alleviate some of the tedious symptoms of parkinsonism. Most of the early efforts consisted of destructive lesions of the pyramidal tract. Neurosurgical operations of the cerebral cortex for involuntary movements were originated by Horsley,[1] who excised the precentral cortex in cases of athetosis as early as 1890. Operations which were devised to resect either the premotor cerebral cortex (area 6) or motor cerebral cortex (area 4) were introduced by Klemme[2] and by Bucy,[3] approximately 20 years ago. Bucy states that cortical extirpation is most effective when it includes cortical area 4 and 6 of Brodman (Fig. 1). This operation

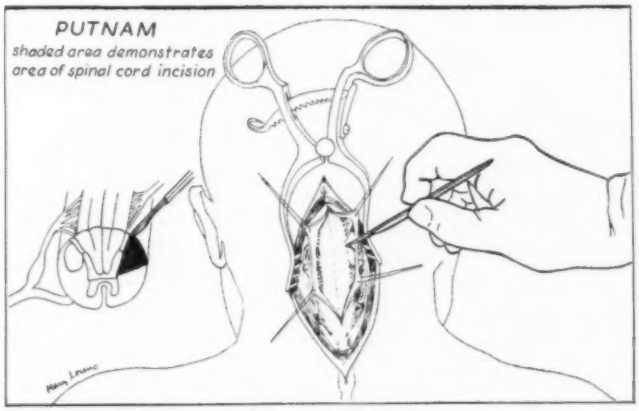

Fig. 2.—Transsection of the pyramidal tract in cervical spinal cord as advocated by Putnam. This operation produces an ipsilateral hemiparesis with proportional reduction of tremor. Rigidity is unaffected.

produces a contralateral hemiplegia which subsequently lessens in severity leaving the patient with a residual hemiparesis but without tremor. Epileptiform seizures may develop following this operation. Rigidity and incapacitation are not decreased and may, in fact, be increased by cortical extirpation.

As a result of his investigation Bucy stated:

> "Nothing in my experience leads me to believe that it is possible to abolish tremor by any procedure which does not interrupt the pyramidal tract or destroy that portion of it which arises from the precentral gyrus."

This conclusion stimulated others to attack the pyramidal tract at levels below the cortex. Putnam[4] devised the operation of pyramidotomy which consists of incision of the pyramidal tract at the level of the second cervical segment of the spinal cord (Fig. 2). Ebin[5] and Oliver[6] have devised modifications of spinal pyramidotomy. Walker[7] has devised an operation upon the pyramidal tract in the cervical peduncle. This operation is referred to as pedunculotomy. According to Walker, a compromise with paralysis and freedom from tremor is the best that can be expected from pedunculotomy or from other operations aimed at the pyramidal tract, either at the cortical or spinal cord level. Such operations were devised solely to relieve tremor and they succeed in

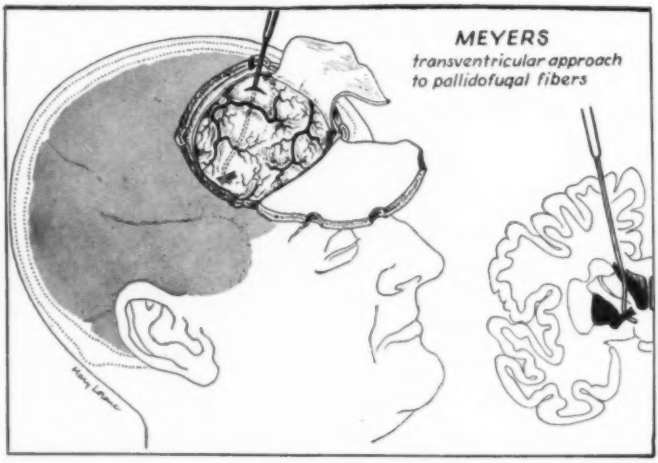

Fig. 3.—Transventricular approach of Meyers to the pallidofugal fibers. This operation was one of the first approaches to surgery of the basal ganglia and demonstrated that tremor and rigidity could be alleviated without necessarily producing loss of motor power.

this aim only at the expense of motor power. It has since been demonstrated that tremor can be relieved without necessarily sacrificing motor power. Thus, there is rarely, if ever, at the present time, any indication for purposeful destruction of the pyramidal tract in the treatment of parkinsonism.

Basal Ganglia Operations: A more profitable neurosurgical target in cases of shaking palsy is the region of the basal ganglia. A major advance in the surgical therapy of parkinsonism was the investigation of Meyers in the surgery of the basal ganglia. Since 1940, Meyers[8] has experimented with various operations among which are: 1) extirpation of the head of the caudate nucleus and interruption of fibers in the oral portion of the anterior limb of the internal capsule; 2) extirpation of the head of the caudate nucleus and the oral one-third of the globus pallidus and putamen; and 3) section of the pallidofugal fibers emerging from the mesial globus pallidus. Meyers has said that "for each of these procedures, it has been possible to demonstate an obvious improvement with respect to tremor and rigidity." He considers pallidofugal section the most effective of these three operations (Fig. 3). Meyers' experience

convinced him that the risks are too great to warrant the general use of transventricular operations in parkinsonism. However, even though Meyers does not recommend his transventricular operation for general use in neurosurgical clinics, his work introduced new concepts into the surgery of parkinsonism.

Browder[9] has developed a modification of Meyers' transventricular operation which he calls the capsular operation. This operation reduces tremor and also to some extent rigidity. Although it initially produces a paralysis of the extremities, Browder states that the paralysis largely disappears although the patient subsequently "shows a lack of interest in using the hand." Browder concludes that fully 90 per cent of patients with parkinsonism are excluded as candidates for this procedure.

In recent years, other basal ganglia operations have been devised. Spiegel and Wycis[10] have produced electrolytic lesions in the pallidofugal fibers by employing a stereotactic apparatus which they develop for operations on the human brain. Narabayashi[11] has devised his own stereotactic instrument to inject procaine in oil into the globus pallidus. Fénelon[12] has devised a direct method for "sub-pallidal" or ansa lenticularis coagulation without use of a stereotactic instrument or roentgenographic control. Guiot and Brion[13] have also carried out direct coagulation of the mesial globus pallidus and ansa lenticularis principally by an opened subfrontal operation. Each of these investigators has reported the alleviation of tremor and rigidity without necessarily inflicting a pyramidal tract lesion or paralysis upon the patient. Detailed and documented long-term follow-up studies of these cases will eventually help to evaluate what assets or deficits each particular technique may have. It is not unlikely that various neurosurgeons will be able to approach the region of the basal ganglia with salutary results employing various techniques. A further period of objective evaluation and perfection of techniques is the only way in which this matter can be clarified.

During the past three years, two original techniques have been developed on our neurosurgical service and have thus far been employed in a personal series of 145 cases.[14-17] I should like to briefly describe each of these techniques, list our current results and to present motion pictures of some of our longer term follow-up cases. In addition, one of the patients who appears in the motion picture is here tonight and will be presented for your own evaluation.

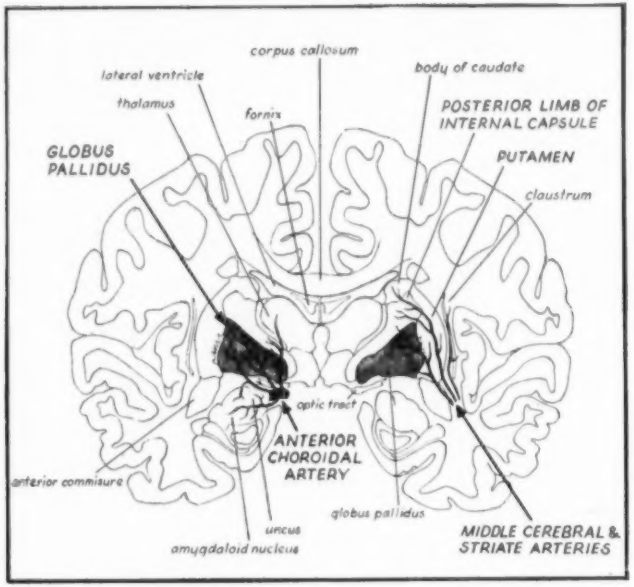

Fig. 4. (a) Illustration of the role of the anterior choroidal artery in the blood supply of the mesial globus pallidus.

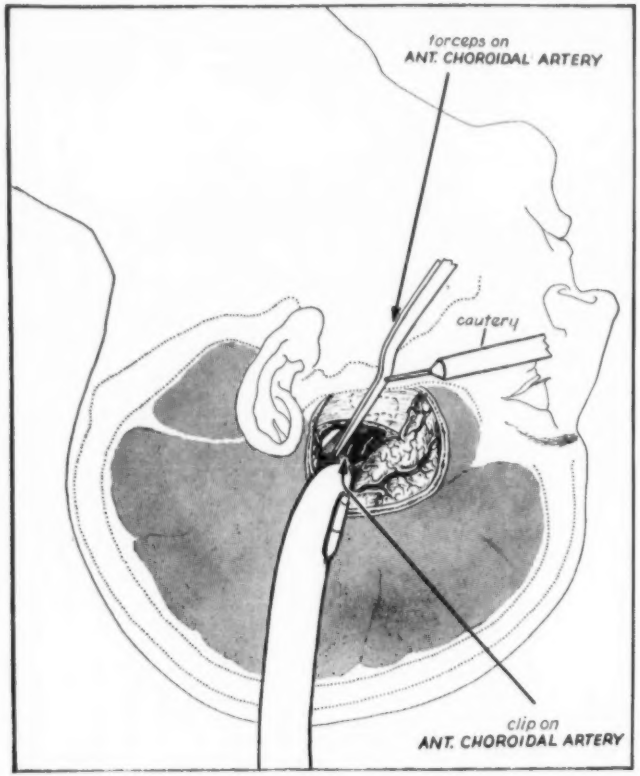

Fig. 4. (b) Surgical approach to occlusion of the anterior choroidal artery. This operation is performed in order to infarct the mesial globus pallidus and certain of its efferent connections.

Surgical Occlusion of the Anterior Choroidal Artery

The anterior choroidal artery has been demonstrated by Abbie to be the principal source of blood supply for the mesial part of the globus pallidus and its efferent connections through the ansa lenticularis with the corpus subthalamicum, ventrolateral nucleus of the thalamus, substantia nigra, and red nucleus. Abbie stated that these structures together with the anterior choroidal artery developed phylogenetically as a "functional unit." It has been our hypothesis that occlusion of the anterior choroidal artery might destroy the mesial globus pallidus, as well as certain other parts of this functional unit. Our surgical investigation has been based upon this hypothesis which was developed subsequent to one case in which the anterior choroidal artery was unintentionally sacrificed.

The surgical details of occlusion of the anterior choroidal artery have been described elsewhere and need not be repeated tonight. The operation can be briefly visualized in the accompanying figure (Fig. 4 a and b).

During the past three years, anterior choroidal artery occlusion has been performed on our own service 55 times. The mortality rate is 10 per cent. There were three cases of hemiplegia. Seventy per cent of the patients in the series demonstrated good results which have persisted up to the present time. This signifies virtual alleviation of tremor and rigidity of the extremities contralateral to the operation without any sacrifice of motor power. In addition, in several instances, there was noted marked improvement in masked facies, gait, speed of voluntary acts and reversal of previous fixed deformities. The operation of anterior choroidal artery occlusion should be limited to patients under the age of 55 with long-standing parkinsonian symptomatology and incapacitation.

Chemopallidectomy

In our search for a neurosurgical technique which could be used not only in young parkinsonian patients but also in geriatric parkinsonians, we have developed a procedure now referred to as chemopallidectomy.[17] This technique too has been described in detail elsewhere and will not be elaborated upon tonight. The fundamental aspects of the procedure can be seen in the accompanying figure (Fig. 5).

In brief, we have developed a relatively simple method for introduc-

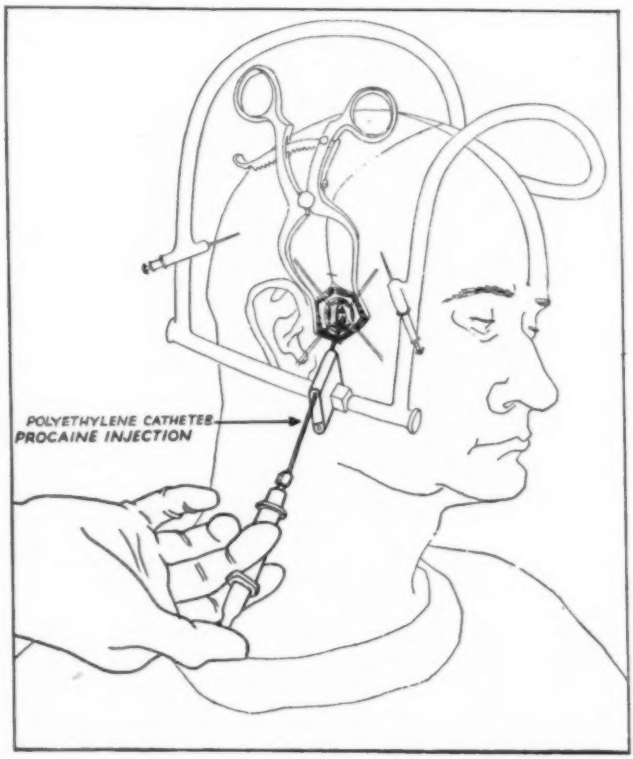

Fig. 5.—Demonstration of pallidectomy guide used during the operation of chemopallidectomy. With polyethylene catheter in the mesial globus pallidus, procaine is injected to determine effect of a lesion in this region upon contralateral tremor and rigidity.

tion of a small polyethylene catheter, either directly by hand or with the aid of a simple six-ounce needle guide we have developed, into the region of the mesial globus pallidus. Procaine is then injected into this region. In this way, the particular site is located, procainization of which will abolish tremor and rigidity of the contralateral extremities. Once the correct site has thus been localized, more lasting results can be achieved by producing a destructive lesion in the same area. We have experimented with several different ways of producing this destructive lesion including electrolysis, radio-frequency current, projection of a small knife blade into the region and injection of absolute

alcohol. The best results which we have obtained thus far have been with absolute alcohol. We are currently employing a solution containing 8 per cent celloidin in 95 per cent ethanol. This solution has the neurolytic properties of absolute alcohol but is viscous and very easily controllable during injection into the brain. Others are currently investigating the use of a small radioactive bead and ultrasonic vibrations to produce intracerebral destructive lesions. Each of these appears to have great potential merit and undoubtedly many technical improvements in all techniques will be forthcoming.

The operation of chemopallidectomy has been performed 90 times. The mortality rate up to this time is 3.3 per cent. Two cases have been complicated by hemiparesis. Seventy per cent of the cases now show good results during the follow-up period of this study. That is, since the time of operation these patients have had alleviation of tremor and rigidity in the opposite extremities. The longest follow-up period for chemopallidectomy is now 18 months, whereas some cases have been followed for three years in the series of patients who have undergone anterior choroidal artery occlusion. The operation of chemopallidectomy has now been employed in many patients between the age of 60 and 65. The operation is tolerated well by selected patients in this older age group and is, as far as I can determine, the first neurosurgical approach which can be used with a reasonable degree of safety in patients in the seventh decade of life.

Rather than describe in further detail the results which have been obtained, I should like to show a motion picture showing six patients before and after operation. The first three patients have been subjected to anterior choroidal artery occlusion and are shown preoperatively and again at various periods up to two years following operation. The second three patients have been subjected to chemopallidectomy and are demonstrated preoperatively and one year postoperatively. It is seen in this film that all of these cases have remained free of tremor and rigidity since the time of surgery and are able to function virtually normally with extremities which were previously incapacitated by tremor and rigidity.

The last patient, a 39-year old man, who, as you have seen in the preceding film, had marked tremor, rigidity and a dystonic deformity of the right extremities for 18 years prior to operation, is here tonight. Since the best way to evaluate any surgical procedure is by evaluating

the results, I have asked this patient to be present so that he could be examined and evaluated personally. As you can see, he is now entirely free of tremor and rigidity of the right extremities and presents no stigmata of parkinsonism. Both arms swing automatically while walking. This patient has gained thirty pounds since operation, and although he had not worked for seven years preceding surgery, he has since been able to return to gainful employment.

The Present Status of Neurosurgical Therapy

It is my opinion, as stated previously, that neurosurgical therapy of parkinsonism has now reached the stage in which it can be considered as a practical, useful, reasonably safe, and rewarding method of therapy in many instances of carefully selected, advanced cases of parkinsonism. However, this is not to say that surgery should be considered in every case of parkinsonism or that it will be successful in every case which is selected for operation.

Certain important scientific steps must be taken in order for neurosurgical techniques in parkinsonism to serve the useful and essential role in the therapy of this disease of which it is potentially capable. These steps are:

1. A new physiologic, diagnostic evaluation of patients with this syndrome. Since parkinsonism is merely a complex of a group of symptoms, a more descriptive and physiologic nomenclature is needed in evaluating each case. Neurosurgical therapy is aimed at specific symptoms and signs of the complex. Therefore, before any patient can be considered as a candidate for neurosurgical therapy, the individual signs and symptoms in that particular case must be carefully assessed, in a more specific way than has heretofore been the rule.

2. An objective, scientific evaluation of the results obtained by various techniques must be forthcoming. So much of the medical literature regarding the possibilities of various therapies for parkinsonism has been beclouded by statements which are not supported by fact, that it is particularly essential that this type of case be assessed in as scientific a manner as possible. To this end, I have arranged for the cases in my own investigation to be examined and appraised objectively by two groups who have not played a part in the development of these particular neurosurgical techniques. Dr. Leonard Diller and his associates are compiling a separate statistical follow-up study on all the patients

who have been operated upon during this investigation. In addition, Dr. Robert S. Schwab, Director of the Parkinsonism Clinic at Massachusetts General Hospital, has accepted my invitation to evaluate personally the follow-up results in the same series of cases. It is my hope that these studies will not only provide an objective evaluation of the results which have been obtained in my own series of cases, but will also serve as a basis for the type of evaluation which is necessary for similar investigations in this field.

Summary

It has been the intention of this presentation to describe the past efforts of neurosurgeons to alleviate the symptoms of parkinsonism and to summarize the status of current efforts. It has also been my purpose to demonstrate by cinematographic records and the presentation of one of our cases in person, the type of result which can be obtained in far advanced cases of parkinsonism by certain neurosurgical techniques. There is still much more unknown about parkinsonism and its therapy than is known at the present time. However, there are certain conclusions which can now be substantiated by fact. These conclusions are:

1. The most profitable approach to the neurosurgery of parkinsonism at the present time is surgery of the basal ganglia, particularly the globus pallidus. Two original techniques which have been used in a series of 145 cases have been described and some of the results presented tonight. As I have indicated, others in this country and abroad have been developing surgical techniques aimed at the basal ganglia and have reported promising and hopeful results.

2. Tremor and rigidity of parkinsonism can be relieved neurosurgically without sacrificing motor power. In my own experience such relief has been demonstrated to persist for as long as three years without any recurrence of symptoms up to the present time. In some cases other stigmata of the disease have been alleviated as well. Not all cases are suitable subjects for surgical intervention. Of those operated upon in our series of cases 70 per cent have received lasting alleviation of tremor and rigidity.

3. In addition to the perfection of surgical techniques, particular attention should be paid to the selection of patients as possible candidates for neurosurgical therapy and to the development of a more useful

classification of patients with the parkinsonian symptom complex.

4. There is a factual basis for judicious optimism regarding the future contributions of neurosurgical therapy to the welfare of patients with parkinsonism. In order for these potentialities to be realized, patients must be cautiously and judiciously selected as candidates for operation and operations of documented merit must be painstakingly performed.

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REHABILITATION IN THE AGED*

HOWARD A. RUSK† and MICHAEL M. DACSO‡

THESE meetings serve as tangible evidence of the wisdom and foresight of those who are responsible for the organization of the Annual Graduate Fortnight. Prompted by the recognition of one of the most important health and social problems of our days, the sessions this year are devoted to the problems of aging.

Among the various medical problems of the aged, physical rehabilitation is one of the most important. Tonight I wish to discuss with you some of the major problems encountered in the rehabilitation of the elderly, chronically ill and handicapped patient.

Chronologically, medical rehabilitation is a comparative newcomer among the clinical disciplines. However, we consider rehabilitation in broader terms as a new medical approach. We realize the need for such a comprehensive approach to the complex difficulties of the handicapped and aged was long overdue in clinical medicine. This new clinical concept actually demands that the practicing clinician no longer consider himself a highly skilled technician, concerned only with the technicalities of physical and mental health, but far beyond this scope recognizes the importance of psychological, social, economic and other factors as important contributors to his patients' well-being.

By tradition the medical practitioner is a repository of his patients' confidence and is often consulted in problems not immediately related to medical matters. A good physician who regards his services in the light of general humanity must be ready to assist those who turn to him for counsel. Here the important question arises–how can he help if he is not properly equipped to render such services. This question is being increasingly realized by medical educators and all those who are responsible for the preparation of the next medical and allied professional generation, and appropriate arrangements are being made to

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extend the scope of medical education beyond subjects strictly technical in nature.

Speaking of rehabilitation, tonight I wish to limit my discussion to medical rehabilitation, emphasizing that no matter how important the clinician's role is in total restoration of a chronically ill and disabled patient he can only be partially successful without making use of the services of a host of highly skilled co-professional workers such as therapists of different types, medical and social workers, psychologists, counselors and others. Total rehabilitation means much more than physical restoration. It means the total integration of the physically restored individual into the dynamic life of the community.

The magnitude of the problem is sufficiently known that extensive substantiating statistical quotations are unnecessary; a few pertinent figures, however, will facilitate readier understanding. The percentage of 65 years and older people in our population has increased from 4.1 per cent in 1900 to 8.1 per cent in 1950 and it is estimated, by at least one source, that by 1980 this figure will grow to 11.6 per cent and will reach 13.2 per cent in 2000. Together with this, the most important fact to consider is the health condition of this sizeable segment of the population.

To illustrate the seriousness of the health situation I will show you a chart prepared by the United States Public Health Service, giving the estimated number of long-term disabled in the United States.[1] This table clearly demonstrates the sudden increase of such patients in the age groups of 55 years and over.

I could go on to quote almost identical figures from other surveys, but this would not serve any practical purpose since it would prove only the same, namely the preponderance of disabling illness among the elderly population.

From the experience of the past few years, we know that many of these seriously disabled people can be restored to self-sufficient existence, or if this is impossible, at least to independent self-care. Even this latter seemingly modest achievement means a great deal in the patient's and his family's life.

For purely practical purposes, admittedly somewhat arbitrarily, we have classified the old people in need of rehabilitation into three groups:[2]

The need for rehabilitation in the first group is obvious and requires no further explanation. Patients of the second group are just as much

TABLE I†—ESTIMATED NUMBER OF PERSONS WITH LONG-TERM DISABILITY IN THE UNITED STATES, BY AGE, 1950

	*Total Population**			*Civilian Noninstitutional Population*		
Age	*Number*	*Number Disabled*	*Per Cent Disabled*	*Number*	*Number Disabled*	*Per Cent Disabled*
All ages	150,697,361	5,298,060	3.51	148,148,202	4,191,000	2.83
Under 5	16,163,571	55,250	.34	16,146,466	50,050	.31
5-14	24,318,953	189,280	.78	24,193,646	147,580	.61
15-19	10,616,598	118,430	1.12	10,305,065	81,410	.79
20-24	11,481,828	158,650	1.38	11,065,168	111,760	1.01
25-34	23,759,267	395,980	1.67	23,224,342	269,400	1.16
35-44	21,450,359	501,790	2.34	21,139,075	353,020	1.67
45-54	17,342,653	712,020	4.11	17,111,081	540,710	3.16
55-64	13,294,595	1,069,480	8.04	13,082,188	886,970	6.78
65 and over	12,269,537	2,097,180	17.09	11,881,171	1,750,100	14.73

* Excluding special units for mental, tuberculosis, and chronic disease patients. Long term patients were defined as those who had been in the hospital 30 days or more at the time of census.

† Table 41—*The States and their older citizens,* page 154, Chicago, Council of State Governments, 1955. Based on United States Public Health Service, Care of the Long-Term Patient: Source Book on Size and Characteristics of the Problem, publication No. 344. Prepared by the Division of Public Health Methods, Public Health Service, United States Department of Health, Education, and Welfare. Reprinted by permission of the publisher.

TABLE II

1. Restoration of the *obviously handicapped* patient (hemiplegia, arthritides, fractures, amputations and neuro-muscular diseases).
2. Restoration of the chronically ill *without signs of a manifest disability* (chronic cardiacs, chronic pulmonary diseases, etc.).
3. Restoration of the elderly person who is not obviously ill but whose *physical fitness* is impaired.

in need of rehabilitation concomitant or following conventional medical care, but unfortunately, in spite of the considerable strides made in the past years, methods of rehabilitating these patients are not as efficient as those of the first group. In the field of cardiac rehabilitation, our department at New York University-Bellevue Medical Center has just started some fundamental exploration. It is planned that this exploratory

work will take the special needs of the elderly patients into serious consideration. The third group in our table includes probably the most neglected group of old people—those who are not sick enough for continuous medical care, but certainly not well enough to perform their everyday functions without difficulty. The well tried rehabilitation methods can serve these patients most advantageously.

To come down to practical measures, I would like to give you a brief description of the procedures we follow in the course of rehabilitation and suggest that a similar pattern should be considered by all those who in the course of their medical activities are called upon to deal with disabled old patients. This I do mindful of the fact that extensive institutional facilities are not always and everywhere available and appropriate modifications will be needed to meet the local needs.

The first important step on the long road leading to successful rehabilitation is the total evaluation of the patient's physical, mental, social, etc., assets. Let me emphasize again that a simple assessment of the physical deficiencies cannot serve as a strong enough foundation for successful total restoration.

In our practice this evaluation is performed by a team of medical and paramedical specialists. Their findings are presented in the evaluation conference where the final recommendations for the rehabilitation program are made. The work-up includes all necessary medical, mental and social information with a strong emphasis on the assessment of the patient's functional abilities. An inventory is made of the essential activities necessary to conduct a self-sufficient life. This A. D. L., as we call it, reveals all deficiencies that require correction. A glance at the specially designed chart will tell you the whole story.

On admission, every patient is tested for the performance of all these activities. If the activity can be performed, the adjoining block is filled in with black pencil; if not, the block is left blank. This initial testing gives us the necessary information about the patient's functional shortcomings and in what direction the training activities should be conducted. If and when, during the training, the patient has learned certain new activities, the adjoining block is filled in with red pencil and the date of first performance is indicated. Thus, a good picture can be obtained of the progress made by the patient. This chart can and probably should be modified according to the individual needs and experience of each institution, but it can be recommended emphatic-

TABLE III—GOLDWATER MEMORIAL HOSPITAL, NEW YORK CITY

Department of Physical Medicine and Rehabilitation

DATE_____

NAME_____ WARD_____ AGE_____ SEX_____

DIAGNOSIS_____

DISABILITY_____ APPLIANCE_____

Method of Recording Test

☐ 1. If at the time of the initial testing an activity cannot be performed independently, leave the block blank.

☐ 2. If activity can be performed, but very slow and labored, fill in one-half block.

☐ 3. If the activity can be performed independently, fill in the block with black pencil .

☐ 4. If the activity is not essential for the person's physical demands, draw diagonal lines in the block.

Method of Recording Progress

☐ 1. When the activity can be performed independently, fill in the block in red and the date.

A. *Bed Activities*
- 1. Rolling to right and then left side.... ☐
- 2. Sitting erect in bed ..... ☐
- 3. Moving forward and backward in sitting position ..... ☐
- 4. Turning body and placing legs over side of bed ..... ☐

B. *Toilet Activities*
- 1. Motion of combing or brushing hair.. ☐
- 2. Motion of brushing teeth ..... ☐
- 3. Motion of shaving or applying make-up ..... ☐
- 4. Motion of washing hands ..... ☐
- 5. Motion of washing face ..... ☐
- 6. Motion of washing body ..... ☐
- 7. Motion of washing extremities ..... ☐
- 8. Motion of removing dentures ..... ☐
- 9. Motion of washing dentures ..... ☐
- 10. Motion of caring for fingernails..... ☐
- 11. Motion of maintaining bed pan..... ☐

C. *Eating and Drinking Activities*
- 1. Motion of cutting meat ..... ☐
- 2. Motion of buttering bread ..... ☐
- 3. Motion of eating with a fork ..... ☐
- 4. Motion of drinking out of a glass.... ☐
- 5. Motion of drinking out of a cup..... ☐
- 6. Motion of stirring coffee..... ☐
- 7. Motion of drinking with a straw..... ☐

D. *Dressing and Undressing Activities*
- 1. Putting on undershirt ..... ☐
- 2. Putting on shirt ..... ☐
- 3. Putting on trousers ..... ☐
- 4. Tying tie ..... ☐
- 5. Putting on socks ..... ☐
- 6. Putting on shoes ..... ☐
- 7. Putting on bra ..... ☐
- 8. Putting on underpants ..... ☐
- 9. Putting on girdle ..... ☐
- 10. Putting on dress ..... ☐
- 11. Putting on stockings ..... ☐
- 12. Putting on coat ..... ☐
- 13. Putting on hat ..... ☐
- 14. Putting on gloves ..... ☐
- 15. Putting on eyeglasses ..... ☐
- 16. Putting on braces ..... ☐

E. *Hand Activities*
- 1. Write name and address ..... ☐
- 2. Fold letter, place in envelope and seal envelope ..... ☐
- 3. Open envelope, remove letter ..... ☐
- 4. Open and close safety pin ..... ☐
- 5. Use dial telephone ..... ☐
- 6. Turn pages of book ..... ☐
- 7. Wind wrist watch ..... ☐
- 8. Strike match ..... ☐
- 9. Manipulation of ..... ☐
  - a) buttons ..... ☐
  - b) zippers ..... ☐
  - c) snaps ..... ☐
  - d) hooks and eyes ..... ☐
  - e) laces ..... ☐
  - f) bows ..... ☐
  - g) ties ..... ☐
  - h) buckles ..... ☐

F. *Wheelchair Activities*
- 1. Bed to wheelchair ..... ☐
- 2. Wheelchair to bed ..... ☐
- 3. Managing brakes ..... ☐
- 4. Raising and lowering foot rests..... ☐
- 5. Propelling wheelchair backward 30 feet and stopping ..... ☐
- 6. Propelling wheelchair forward 30 feet and stopping ..... ☐
- 7. Opening and closing door in wheelchair ..... ☐
- 8. Wheelchair to chair ..... ☐
- 9. Chair to wheelchair ..... ☐
- 10. Washing at sink ..... ☐
- 11. Wheelchair to toilet ..... ☐
- 12. Toilet to wheelchair ..... ☐
- 13. Wheelchair to bathtub ..... ☐
- 14. Bathtub to wheelchair ..... ☐
- 15. Wheelchair to automobile ..... ☐
- 16. Automobile to wheelchair ..... ☐
- 17. Wheelchair to floor ..... ☐
- 18. Floor to wheelchair ..... ☐

G. *Elevation Activities*
- 1. Bed to erect position ..... ☐
- 2. Erect position to bed ..... ☐
- 3. Wheelchair to erect position ..... ☐
- 4. Erect position to wheelchair ..... ☐
- 5. Chair to erect position ..... ☐
- 6. Erect position to chair ..... ☐
- 7. Erect position to toilet ..... ☐
- 8. Toilet to erect position ..... ☐
- 9. Erect position to tub ..... ☐
- 10. Tub to erect position ..... ☐
- 11. Down to floor ..... ☐
- 12. Up from floor ..... ☐
- 13. Pick object from floor ..... ☐

H. *Special Hand Activities*
- 1. Open and close cylinder lock..... ☐
- 2. Open and close ice box door..... ☐
- 3. Open and close drawers ..... ☐
- 4. Open and close doorlock with key.... ☐
- 5. Open and close door hook ..... ☐
- 6. Open and close window ..... ☐
- 7. Pull window shade ..... ☐
- 8. Work shop switch ..... ☐
- 9. Work plug switch ..... ☐
- 10. Work push button or bell ..... ☐
- 11. Work pull chain light ..... ☐
- 12. Open and close cabinet lock..... ☐
- 13. Turn 4-pronged faucet ..... ☐
- 14. Turn circular faucet ..... ☐
- 15. Open and close medicine chest..... ☐
- 16. Open and close bottle ..... ☐

I. *Walking and Climbing Activities*
- 1. Walking forward 30 feet ..... ☐
- 2. Walking backward 10 feet ..... ☐
- 3. Walking sideward 10 feet ..... ☐
- 4. Opening door, walking through and returning ..... ☐
- 5. Up 15-degree ramp, 3 feet ..... ☐
- 6. Down 15-degree ramp, 3 feet ..... ☐
- 7. Up and down one flight of stairs, one hand rail ..... ☐
- 8. Up and down one flight of stairs, no hand rail ..... ☐
- 9. Up standard curb ..... ☐
- 10. Down standard curb ..... ☐
- 11. Up bus steps ..... ☐
- 12. Down bus steps ..... ☐

J. *Traveling Activities*
- 1. Cross standard street on green light.. ☐
- 2. Get in bus, place coin in turnstile.... ☐
- 3. Go through turnstile and stand holding on overhead strap ..... ☐
- 4. Sit down and get up from bus seat... ☐
- 5. Travel to middle door of bus..... ☐
- 6. Descend from bus to street ..... ☐
- 7. Walk to taxi, 10 feet, open door and enter cab ..... ☐
- 8. Descend from cab, close door and walk 10 feet ..... ☐
- 9. Walk forward 300 feet with package.. ☐
- 10. Carry cafeteria tray with dishes.... ☐

ally that it should be made a part of medical records in every institution dealing with handicapped or chronically ill elderly people.

After such thorough analysis the training starts. The time and place are not appropriate to demonstrate the technicalities of these training procedures. Provisions were made in the program for participation in rehabilitation clinics for those who are interested in observing how these rehabilitation principles are applied in practice. The Institute of Physical Medicine and Rehabilitation, Goldwater Memorial and St. Barnabas Hospitals offer such clinical instruction. I suggest that you consult your program and participate in these clinics. In due course of rehabilitation training, patients improve. To assess the degree of improvement an A.D.L. re-testing is done, and depending on the outcome of this test, the patient is either continued on a program (often with modifications) or if he reached maximum benefit, the emphasis is shifted to his social and vocational problems and his formal integration into the community begins. These are the highlights of rehabilitation mainly emphasizing the benefits that the *individual* derives from such treatment. Allowing that the patient's personal gain is most important, we cannot and should not disregard the benefits of rehabilitation on the *community* and its hospitals and other patient care institutions.

The role and effect of comprehensive rehabilitation in the community and its hospitals are not sufficiently recognized and I would like to, if I may, spend some time discussing some of these problems, not as a hospital administrator, but rather as a clinician who makes his observations at the patient's bedside where these problems actually arise.

It has been a matter of common knowledge to all of you who freely give your professional services to the public hospitals, that a varying, but always sizeable proportion of your patients in the wards are, strictly speaking, in no need of hospitalization. This contention was substantiated by a recent study,[3] conducted by the staff of the Department of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center at the Rehabilitation Service of Goldwater Memorial Hospital. The study group consisted of physicians, social workers, psychologists, nurses, occupational and physical therapists and, as an unusual feature, the hospital chaplains were also consulted. A total of 95 unselected custodial patients were surveyed and the results were published in a monograph which is available to all those who are interested. The most revealing and dramatic finding was the unanimous considered opinion

of the study group that, out of the 95 patients (whose average age was 68.5 years) only seven were felt to be in need of continued hospitalization; and two of these cases were considered to be questionable. Using our customary rehabilitation standards, 11 patients were considered suitable for training with a prospect of successful rehabilitation better than 50 per cent. The remaining 84 of the original 95 patients were considered to be in no need of either definitive medical care or rehabilitation. Although the disability diagnosis included such conditions as hemiplegia, paraplegia, quadriplegia, hip fractures, amputation, etc., all these patients were in such a condition, that in spite of the grave-sounding diagnoses, continuing hospitalization was not considered necessary. The 95 patients surveyed spent a total of more than ¼ million uninterrupted days in municipal hospitals. Using conservative calculation the financial loss borne by the city in this small group of patients was in the realm of millions of dollars. The cost in human values, boredom, anxiety, frustration and resignation is incalculable.

To illustrate this situation, I will give the brief histories of three patients from the survey. These cases, illustrative as they are, are by no means unique or unusual.

1. M. C. is a 52-year-old white female who has spent a total of 8,401 days in different municipal hospitals. She was admitted in 1930 at the age of 28 with a diagnosis of rheumatoid arthritis and in spite of the fact that she had a husband and daughter living in the city, she continuously remained in the city hospitals for more than 23 years. Her arthritis was inactive; she was bedridden and could have been cared for perfectly adequately at home or in a nursing home. This was hospitalization for convenience.

2. M. B. is a 67-year-old colored female who had a hemiplegia as a result of a rupture of the middle cerebral artery in 1936. She was cooperative, alert and completely ambulatory. She not only took care of herself, but assisted other patients and did chores around the ward. She was hospitalized since early 1936 with a three-year interruption when she stayed with her sister. Up to the date of the survey she had spent 3,412 days—that is almost 10 years—in municipal hospitals. She was in no need of hospitalization.

3. B. O. is a 66-year-old white male who suffered from paraplegia of unknown origin. He was hospitalized continuously in public institutions since 1934. Total days of hospitalization 7,035; that is, almost

20 years. This patient was able to take care of himself from the wheelchair and was in no need of hospital care. In fact if our modern concept of paraplegic care had existed in 1934, this patient could have gone to work after an average training period of 120 days.

These three patients alone have been cared for in municipal facilities for a total of nearly 19,000 days. Calculating arbitrarily and conservatively at $12 per diem, the total cost for *these three patients alone* is $228,000, and the end is not in sight.

This survey suggested the necessity of studying this situation on a larger scale. Through the generosity of the New York Foundation, which incidentally supported the first Goldwater study, a large scale survey is now in progress: a joint project between the Department of Physical Medicine and Rehabilitation of New York University-Bellevue Medical Center and the Department of Hospitals, which when finished will give a reliable picture of the number and natural history of the custodial "patients" at the present unnecessarily in municipal hospitals. Although the survey is still in progress and the findings are not tabulated, I do not believe that I am mistaken or indiscreet when I say the first impression of the survey group supports the views of some previous investigators inasmuch as they feel that one of the main factors responsible for the disproportionate accumulation of custodials in the municipal institutions is the confusion that exists around the separation of chronically ill from the custodial. Not realizing that among the many other differences between these two groups there is a rather decisive one,—namely, their need for active medical care,—a commodity that is so precious and of which the custodials can make but very little use. Without over-simplifying this issue, it can be safely said, this single factor is sufficient to exclude a large number of so-called custodial patients from public hospitals. The other large group of patients in acute and chronic general hospitals are those who have been there, sometimes for years, for some physical disability. Many of these people could easily be returned to the community if the hospitals had well organized rehabilitation departments. It can be said that an important function of the rehabilitation department in a hospital is that of a safety valve which prevents it from clogging up with custodials, and by restoring the "hard core" patients, assures a more economical and efficient use of beds.

The greatest obstacle in the way of establishing rehabilitation services in hospitals is the critical shortage of professional personnel. Although the

need for trained professionals extends along the entire roster of medical and paramedical specialists, today I will briefly touch only on the need for specially trained physicians. In spite of the fact that at the present our medical schools have a capacity of 7500 students each year, as compared with 5500 at the end of World War II, in many medical specialties and some geographical areas there is still a critical shortage of physicians. The most pressing shortage exists in specialists in physical medicine and rehabilitation, psychiatry, public health, and administrative medicine. All these specialties are vitally important in the care of the aging. This simple fact indicates one of the important aspects of the difficulties in medical care of the aging. I wish to emphasize, however, that with the cooperation of all concerned, in the first place the medical profession, all these problems can be solved. The majority of the medical profession has long ago abandoned its initial reservation towards rehabilitation and accepted it as full partner in the total effort of the service to the sick. If this acceptance could be emphasized in the field of the medical care of the elderly, these often neglected people would enjoy a great many new benefits.

While we meet here today an important event is taking place in Albany, which in all probability will have a decisive effect on the care of the aged in New York State. I am referring to the Governor's Conference which has been meeting this week in the State Capitol. To this Conference, people from all walks of life have been invited to contribute their best knowledge to the medical, social and other welfare problems of the aging citizen. From all evidences this conference will be most successful and I have reason to believe that recommendations made by this group of experts will materially benefit the elderly population of this State.

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SYMPOSIUM ON ACUTE ANTERIOR POLIOMYELITIS

Presented at the Meeting of the Section on Pediatrics at The New York Academy of Medicine November 10, 1955

POLIOMYELITIS VACCINE: *Some Considerations Relating to Its Safety**

JAMES A. SHANNON** AND CARL L. LARSON***

I AM grateful for this opportunity to come before you and discuss a subject of mutual interest—the production and safety of poliomyelitis vaccine. Certainly this matter is of particular interest to pediatricians, who will administer the bulk of the vaccine, as it is to us of the Public Health Service who must attest to its "purity, potency, and safety" under the Biologics Act of 1902. I will review some of the technical problems of vaccine production and testing as these developed before the general licensing of the product and shortly thereafter, when an outbreak of poliomyelitis occurred among children who had received vaccine distributed by one of the manufacturers. I will also discuss certain more recent developments that have resulted from a searching inquiry conducted this summer and fall by the Technical Committee on Poliomyelitis Vaccine.†

* Presented by Dr. Shannon before the Section on Pediatrics at The New York Academy of Medicine, November 10, 1955.
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† The members of the Committee, which is under Dr. Shannon's chairmanship, are as follows: David Bodian, M.D., Poliomyelitis Laboratory, School of Hygiene and Public Health, Johns Hopkins University; Thomas F. Francis, Jr., M.D., School of Public Health, University of Michigan, and Director, Poliomyelitis Vaccine Evaluation Center; Carl L. Larson, M.D., Director, Division of Biologics Standards, National Institutes of Health; Jonas E. Salk, M.D., Virus Research Laboratory, University of Pittsburgh; Richard E. Shope, M.D., Rockefeller Institute for Medical Research; Joseph E. Smadel, M.D., Scientific Director, Department of Virus and Rickettsial Diseases, Army Medical Services Graduate School, Walter Reed Army Medical Center.

Background: The vaccine as prepared for the field trial in 1954 was an experimental product made for the National Foundation of Infantile Paralysis by commercial producers according to the specifications of Dr. Jonas Salk and associates.[1,2] After some initial difficulty, the industrial firms were able to turn out a suitable product, and the field trial was carried out successfully. The results of the field trial were announced on April 12, 1955.[3] On that date, the Public Health Service with the advice of a panel of senior consultants issued official Minimum Requirements,[4] and six manufacturers that had produced vaccine under the earlier provisional requirements were granted licenses.

On April 26, six cases of poliomyelitis were reported among children who had received vaccine manufactured by the Cutter Laboratories. The ensuing investigation of the Cutter Laboratories was later extended to the entire industry and led to a temporary suspension of the nationwide vaccination program. Meanwhile the Public Health Service, on April 28, established a Poliomyelitis Surveillance Unit within its Communicable Disease Center in Atlanta, Georgia. This unit with collaborating state authorities investigated all reported cases of poliomyelitis, more particularly those associated with vaccine. The epidemiological data so developed clearly defined the Cutter incident as an outbreak with characteristics of a common-source epidemic.

This was the take-off point for a study of the vaccine—primarily the premises underlying the process and the extent to which it was amenable to application in routine large-scale manufacturing. The study can best be understood if I take a few minutes to review the vaccine's characteristics and their effect upon its production in the fall and winter of 1954-55.

Basic Procedures: In the production of the Salk vaccine, the basic procedures are the tissue culturing of three types of virus and their inactivation without excessive loss of potency. One strain of poliomyelitis virus has been selected for each type of poliomyelitis vaccine included in the final product. The current Salk formula recommends the Mahoney strain for Type 1, the MEF strain for Type 2, and the Saukett strain for Type 3. In the selection of these strains, the primary characteristic considered was their antigenicity.

Poliomyelitis virus of each type is propagated in a mass-production procedure by seeding minced or trypsinized monkey kidney tissue suspended in nutrient media with live virus. Shed virus is harvested by

simple filtration.

The procedure recommended for production involves inactivation of each single-strain suspension in 1:4000 formaldehyde, at 37° C at pH 7.0, for a period of time that provides for anticipated destruction of infectivity.

The process of inactivation was believed to follow the course of a first-order reaction yielding a straight line when the log of the viral concentration is plotted against time.[1,2] The course of the reaction is measurable with moderate precision during its initial phase, and it is postulated that a continuation of the reaction could be described by extrapolation of the straight line into ranges of viral concentration that are not measurable (Figure 1).

It was initially recommended that the inactivation treatment should be continued over a period equal to three times the period from zero time to the curve intercept at zero. Negative tissue-culture tests were anticipated during the latter portion of this period.

In producing the final vaccine, equal volumes of single-strain pools from each type of poliomyelitis virus are mixed. This mixture is termed a polyvalent or trivalent pool. Trivalent pools were judged suitable for manufacture of vaccine if they passed a second safety test consisting of monkey and tissue-culture tests in which at least 0.1 per cent of the total trivalent-pool volume was used as a sample. Testing is also directed toward the exclusion of B virus, bacterial contamination, and other considerations.

Analysis of Basic Procedures

Inactivation: An important feature of the Salk conception of a suitable vaccine lies in the principle which presumes a large margin of safety built into the inactivation process itself. Figure 1 shows the theoretical course of an inactivation process starting with a concentration of tissue-culture infective doses of 1.0×10^6, a common concentration. During the initial phase of the inactivation process, the log of the virus falls linearly with time, reaching zero some time between 48 and 72 hours. The concentration of live virus is then about 1.0 tissue-culture infective unit per ml. of viral suspension. The chart has been drawn to show the intercept time of the inactivation curve and log zero at three days.

Extrapolating the course of the reaction as a straight line into areas

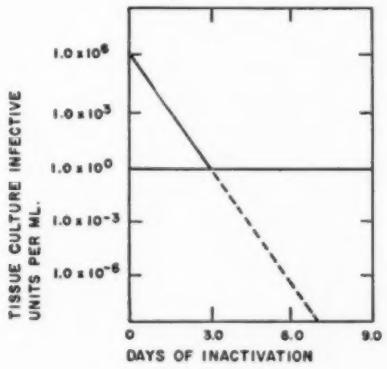

Fig. 1

of low viral concentration, the concentration is of such a low order that its significance can be grasped only when the numbers are reduced to common terms. If the reaction proceeds as initially postulated, there should be a concentration of live virus in the order of one tissue-culture infective unit in each million tons of inactivated viral suspension at the end of nine days.

There are alternatives, however, to this theoretical conception. A viral suspension is not in fact a monophasic system. It consists of a number of discrete particles in suspension. At high concentrations of virus, such a system may behave in a manner not dissimilar to a monophasic system. Thus, during the first part of chemical inactivation, the process may appear to behave as a simple first-order reaction. But as the reaction progresses and at lower virus concentrations, the heterogeneity of the system could well begin to assert itself and the initial description of the reaction no longer obtain.

This residual live virus will probably consist of particulates of varying size and shape and in varying degrees of aggregation. Large particulates, should they be contained in such a mixture, cannot be expected to inactivate at the rate calculated from the behavior of the reaction during its initial phase. During this initial phase, the rate of the reaction will be dominated by that portion of the particulates which compose the bulk and which are most easily inactivated. The extent to which the inactivation process departs from a straight line even in the initial phase of the reaction will be a reflection of the extent to

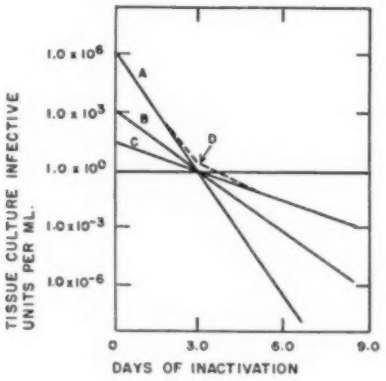

Fig. 2

which the viral suspension is composed of complex particulates of differing over-all sensitivity.

Relevance to Margin of Safety: These considerations have a practical bearing on the manufacturing problems, since heterogeneity that results in variation in the sensitivity of particulates to formaldehyde can operate to remove the so-called built-in factor of safety. This consequence, in a simplified example, is demonstrated in Figure 2.

Curve A describes the inactivation reaction proceeding at a commonly observed rate, the initial concentration of live virus being 1,000,000 particles per ml. (1.0×10^6). Curve B describes a similar reaction proceeding at a rate one-half as fast as Curve A, the initial live-virus concentration of these particles being 1000 per ml. Curve C describes a situation in which the rate of another set of particles is one-fourth of A, the initial live-virus concentration of this set being 32 particles per ml. The composite inactivation curve of a mixture of the three is given as Curve D. Starting with a suspension composed of the three types of particles in the assumed concentrations, the summation of the three reactions will be dominated by the reaction rate of A initially and by C at a later time.[5]

Viewed in this light, it may be concluded that observations on the initial phase of the reaction cannot be taken as the determining basis for predicting the remaining course of the reaction.

There are additional factors that might be operative and that might bear on the interrelated combination of inactivation and safety. The

suspending solution contains protein, coagulable by formaldehyde, which might favor the formation of viral particulates occluded in protein precipitates not generally distinguishable visually. Such particulates would be in a position of relative inaccessibility to formaldehyde.

The extent to which a combination of these factors influences the course of inactivation will also be reflected in the extent to which the total curve of actual inactivation departs from that of a first-order reaction. Unfortunately, the total curve is not measurable.

Analysis of Safety Testing: A safety test, generally speaking, is a laboratory procedure utilized as part of quality control of a product to separate that which is unsuitable from that which is suitable for the use intended. A major factor of safety, according to the original conception, was built into the process of inactivation. The safety tests were designed to demonstrate contamination resulting from accidents in manufacture as well as residual live virus, which the process was believed to reduce to an immeasurably low and harmless level. However, insofar as the process departs from the theoretical conception, whether because of deficiency in conception or because of inadequacies in the handling of the process, the testing becomes of increasing importance both as a guide to processing and as a final determinant of safety.

Two tests are used to determine the presence or absence of live virus in the quality control of the vaccine: the tissue-culture test and the monkey test.

The tissue-culture test had not been examined prior to April 1955 in a manner that permitted an estimation of its sensitivity. That is to say, it had not then been determined at what concentration of infective particles and under what circumstances a positive demonstration of live virus could be expected in a significant proportion of tests run. The psychology of last spring seems to have made this an unessential.

More recently, however, certain assumptions were made as a basis for analysis of the sensitivity and reliability of the tissue-culture test.[5] These will in general provide an estimate of reliability higher than actually obtains. The assumptions were as follows: 1) Residual live virus can be defined in terms of the number of discrete infective particulates contained in a unit volume of antigen suspension; 2) random distribution of these particulates obtains; 3) one infective particulate is an effective dose for a sensitive tissue-culture preparation; and 4) the

TABLE I.—SAMPLE SIZES REQUIRED AT SPECIFIED LEVELS OF CONCENTRATION, MOST SENSITIVE TEST

Probability of Negative Test	*Assumed Concentration of Infectious Units Per Liter*		
	5	*10*	*100*
.10	460 ml.	230 ml.	23 ml.
.05	600	300	30
.01	920	460	46
.001	1380	690	69

TABLE II.—SIZE OF SAMPLES USED PRIOR TO MAY 22, 1955

Laboratory	*Size of Sample (ml.)*	*Chances of Picking Up Positive Lot*
A	210	70%
B	1360	99
C	1600-2100	99+
D	325	80
E	180	65
F	1500	99.9+

volume of virus suspension is no less than ten liters.

With appropriate statistical theory, using the Poisson distribution, applicable in this case, certain probabilities were calculated. These are summarized in Table I, which shows the probability of failure to demonstrate the presence of live virus at different levels of concentration when different size samples are tested. If the upper level of acceptable viral concentration is set at five infective units per liter, the chances of picking up such a positive lot using the volumes commonly tested by each of the manufacturers prior to changes in the minimum requirements were as given in Table II.

It is apparent that different standards of acceptability as regards the possible presence of infective particles were inherent in the processes of the different manufacturers under the April 12 requirements. This

TABLE III.—PER CENT OF SINGLE STRAIN LOTS TESTING POSITIVE

Laboratory	*No. Lots*	*Per cent Positive*
All Labs.	812	11%
A	97	21
B	237	19
C	85	8
D	267	5
E	126	2

variation was possible under those requirements because of their provision that the minimum volume used in the test should be directly proportional (0.1 per cent) to the total volume of the pool under test. Established statistical principles indicate, however, that to ensure with a high degree of probability that the concentration of live-virus particles in any lot will be below a prescribed level, a sample of fixed minimum size must be tested, rather than one proportional to the size of the lot. The calculations assume that no lot contains less than ten liters.

MANUFACTURING EXPERIENCES

Let us turn now to the experience of industry to determine the extent to which these theoretical considerations were applicable. In manufacturing practice, the process of inactivation of the poliomyelitis virus was often characterized by a curvilinear rather than a straight-line relation between time and the log of the residual live-virus concentration in the initial phases of the reaction. This was also evidenced by the occurrence of positive tissue-culture tests from 9 to 12 days after the beginning of the inactivation process.

It was also apparent that the inactivation process had not been carried out in such a way as to yield consistent results in the hands of some members of the industry. That is to say, the initial test performed at the time when virus was expected to have been inactivated showed that an appreciable proportion of single-strain pools still contained live virus. The extent of this is summarized in Table III. This was an important finding. It demonstrated that the departure of the process

TABLE IV.—PER CENT OF POLYVALENT LOTS TESTING POSITIVE

Laboratory	*No. Lots*	*Per cent Positive*
All Labs.	127	13%
A	21	33
B	34	9
C	22	23
D	8	—
E	42	4

from one of systematic predictability greatly diminished the factor of safety believed to be inherent in the basic process. Consequently, principal reliance had to be placed upon the results of the tissue-culture tests for the exclusion of live virus in the final vaccine.

A second feature of the data may be seen by examining the safety tests performed on the trivalent pools immediately after combination. A summary of this is given in Table IV. It will be seen that live virus was frequently found in a trivalent pool when this had been presumed to be free of live virus on the basis of testing the monovalent pools that composed it.

It had to be concluded, therefore, that the tissue-culture test for active virus, as applied to the single-strain pool under the minimum requirements of April 12, was not an adequate process guide, nor did it provide sufficient assurance that live virus was not present in the trivalent pool in unacceptable concentrations. This emphasized the need to modify the tissue-culture tests for processing purposes and to fortify the final safety test performed on the trivalent pool before subdivision and packaging.

A third feature of the data, which can be seen more readily in the detailed rather than the summary tables, is an almost random distribution of positives in relation to the processing data of certain of the manufacturers. Positive tests had occurred in a sufficiently high proportion of cases to minimize the reliability of a single subsequent negative test, whether used for processing control purposes or as a final indication of safety of the trivalent pool.

Formulation of Amended Requirements (May 1955)

As a result of the considerations so far discussed, it has been possible to develop modifications of the requirements controlling the manufacture of poliomyelitis vaccine as these relate to safety.[6] A method that allows a concentration of live virus at no more than five tissue-culture infective units per liter once in a hundred thousand lots is believed to be a satisfactory objective and one within reach. Safety testing and processing have been revised to achieve this objective as follows.

Single strain pools are now inactivated with 1:4000 formaldehyde at 37°C for such a period of time as will permit two consecutive negative tissue-culture tests on samples separated by a three-day interval prior to the termination of inactivation. In order to ensure the exclusion of live-virus particulates above a minimal concentration, the volume of a single-strain pool used for each safety test must be not less than 500 ml.

The trivalent pool is to be considered suitable for vaccine manufacture if a negative tissue-culture test is obtained utilizing 1500 ml. of the pool in the tissue-culture test and employing two different tissue culture preparations.

As a final safeguard against accidental breaks in the over-all production routine, the manufacturer is required to test a random sample of vaccine from final containers of each lot for live poliomyelitis virus. The monkey safety test has been shifted from its previous position, where it was applied to the trivalent pool, and has now been adapted for use as the final-container test. At least five monkeys are inoculated with samplings of each filling lot, and there must be a minimum of 20 monkeys for each manufacturing lot from which these fillings are derived.

Tests made on these animals include tests for potential susceptibility, which requires the demonstration of the absence of circulating antibody in the serum prior to inoculation. In addition, samples of spinal cord segments are removed after 18 days for histologic study and to permit attempts to isolate virus in cases that are histologically questionable. An effort has been made to increase the sensitivity of the monkey test by increasing the susceptibility of the test animal, by increasing the number of monkeys used, and by injecting each animal with vaccine

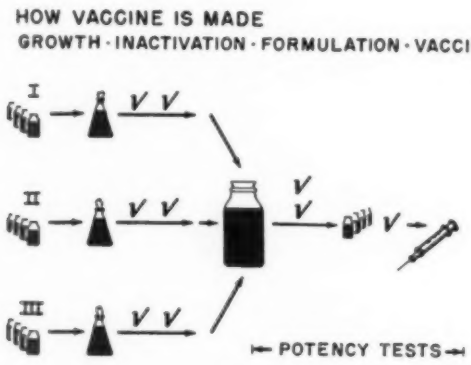

Fig. 3

not only intracerebrally, but also intraspinally and intramuscularly. To increase the susceptibility of the animal, the virus injections are accompanied by injection of 200 mg. of cortisone acetate into the left leg muscles and of 1 ml. of procaine penicillin into the right arm muscles.

As an additional safety test, conducted to establish the potency of vaccine administration via the route usually used in man, 12 monkeys are inoculated intramuscularly, each with 3 ml. of undiluted vaccine given in divided doses and at weekly intervals. These monkeys were formerly considered only as part of the potency test, but can now be considered as an integral part of the monkey safety-testing scheme. They receive an additional intracerebral injection and are studied histologically for evidence of lesions in the spinal cord.

The entire production and testing process is represented in Figure 3. Individual tests are indicated by checks, the final check in the process representing the monkey test. Potency tests are performed at any time after combination of the single-strain pools.

Application of the Revised Requirements: The application of the new requirements to the production of poliomyelitis vaccine was expected to result in a product essentially free of live virus. Negative results at the recommended test volumes in two consecutive tests during initial inactivation or following a single reinactivation period for each single-strain pool, and a third negative following the mixture of the

pools to form the trivalent pool, should ensure that the final vaccine contains five or more infective particulates per liter less than once in 100,000 times.

Additional operational refinements were believed possible in the routine production of the vaccine which should result in further improvements in product, lessening of costs, and no loss in safety. The contemplated refinements have been discussed with the manufacturers at length. These included the substitution of a less virulent Type-1 strain for the Mahoney strain. This should be in effect for next fall's vaccine. Other contemplated refinements are control tests to document sensitivity of tissue cultures, concentration of the viral suspension before applying the safety tests, the conduct of the safety tests themselves, and modification of physical arrangements during processing. Each of these requires further developmental research prior to application.

The application of the new minimal requirements met with outstanding success in one respect but not in another. It succeeded in placing a safe vaccine on the market, as judged by its use in more than seven million children. However, the inability of some of the manufacturers to produce in quantity resulted in a continuing shortage of vaccine in terms of the national need and demand.

On May 26, 1955, the Surgeon General appointed a Technical Committee on Poliomyelitis Vaccine. The responsibility of this Committee was twofold. First, it was to advise, on a lot-by-lot basis, on the release of vaccine for public use. Second, it was to establish and conduct with industry and our Division of Biologics Standards a collaborative study, developmental in nature, aimed at bringing into being at as rapid a rate as possible the several advances in vaccine production and testing that were envisioned in the initial investigation of the problem. The objective was not only an improved product, but the breaking of bottlenecks that impaired volume production. The bulk of the work has been performed by industry, with leadership in the collaborative effort being furnished by Technical Committee members. The details of this work will shortly find their way into the scientific literature.

Generalizing, one might say that studies completed or under way seem to have solved a number of problems of critical importance.[7]

As to safety, we believe the revised tissue-culture safety test has operated effectively, and that the new monkey test will enhance greatly the sensitivity of the procedure.

Abundant evidence is available to the effect that the particles of protected virus postulated in the June technical report do, in fact, exist. It is now known, however, that suitable filtrations placed at strategic points in the manufacturing process can obviate this difficulty.

The combination of process and safety improvement makes, we believe, the presence of the Mahoney strain in the current vaccine less critical. However, as still another added factor of safety, it can and will be replaced—but this will require more time to evaluate the many factors involved in a process as complex as this.

In summary, then, one might say that under the Technical Committee's leadership, industry has demonstrated, after a very trying period, that it can produce a vaccine effective in practice, and we are assured that an adequate amount can be produced under the present requirements.

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PROPERTIES OF AN "IDEAL" POLIOMYELITIS VACCINE*

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NATURE has provided us with certain clues about natural immunity reactions in poliomyelitis which might serve as a guide for those who are planning programs of artificial immunization.[1] It may be worth while therefore to review first, the manner in which nature immunizes man against clinical poliomyelitis today, and how this took place yesterday,—by which I mean two or more generations ago. Let us assume primarily that most of us acquire an inapparent (or clinical) infection to at least one of the three types of poliomyelitis viruses. This would amount to a minimum of one infection and a maximum of 3 + n infections, with 3 standing for the possible number of primary infections and n for the number of reinfections, whether homotypic or heterotypic, that we usually acquire in a lifetime. Although this process has been studied to a limited extent in the chimpanzee, the degree to which man is reinfected homotypically or heterotypically has not been measured on a scale of statistical adequacy, or over a long enough period of time. What one can say with some degree of assurance is that a complex problem exists there, which when elucidated will tell us more about lasting immunity in poliomyelitis.

If we look at this problem—or process, which is going on in our own communities all the time, we find that today in the United States, a leisurely, or what might be called a delayed process of natural infection and immunization against clinical poliomyelitis exists. Thus, most adults here do not become immune to one, two, or occasionally all three types of poliomyelitis virus until they are 25 or more years old. In certain other places this process goes on much faster and more thoroughly. Children or even infants, become immune to all three types of virus

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within the early years of life. Apparently this latter process must have been more common, or indeed almost universal throughout the world 50 to 75 years ago, when poliomyelitis was an infantile disease—the old-fashioned "infantile paralysis." But today such populations of young children, heavily immunized in the natural way, are to be found only in places where sanitation is primitive. One of them, studied recently by the Yale Poliomyelitis Study Unit, represented a group of village communities in the neighborhood of Cairo, Egypt,[2,3] another was the urban community of Casablanca, Morocco.[4] In these North African communities 90 to 100 per cent of children are born with neutralizing antibodies to several types of poliomyelitis viruses as a result of transplacental passage of maternal antibodies. These *passive* antibodies are lost in the first six months of life, but the infants acquire active infection almost at once thereafter. This is indicated by the speed with which their *acquired* antibodies develop. By two to four years of age, over half the children in French Morocco have acquired antibodies against all three types, and by five to nine, the per cent is over 80! Thus, in this population, natural immunity which is apparently acquired by having a series of infections early in life and close together, is solid against reinfection by any type of poliomyelitis virus and well established by the age of 10 or 12. What is the end result? Acute paralytic cases of poliomyelitis in individuals born and raised locally are limited to the youngest age groups; adult poliomyelitis is practically unknown; and large epidemics, in the sense that we know them in the United States and in Scandinavia, are unknown.

In the absence of a vaccine this might seem to be a more desirable situation than ours, if it were not for the fact that these North African infants acquire their solid immunity at a price. This price can be described crudely by the statement that a certain unknown percentage of infants do acquire sporadic or endemic paralytic poliomyelitis, the old fashioned *infantile paralysis*. Just what the case incidence rate is or the mortality rate, has not been determined. Furthermore of course, the circumstances under which poliomyelitis viruses are disseminated throughout the community and allowed to infect infants are the same circumstances which spread the agents of enteric infections and certain other undesirable diseases. The result is that typhoid fever rates are high, the infant mortality rates are high—a very un-American situation.

In contrast to the situation in Morocco is the state of affairs in the

United States.[5] Here exposure and infection are suppressed in early life, and during childhood it occurs much more slowly. Antibodies (and immunity) to all three types of polioviruses are not acquired by the *majority* of North American children until they have reached their teens or even adulthood. With so many susceptibles in the population, epidemics are understandably common, and paralytic and nonparalytic cases in adults have increased steadily since 1900.

One can study this situation indirectly through the medium of antibody prevalence in the different age groups. The acquisition and persistence of neutralizing antibodies seem to parallel the clinical immunity against poliomyelitis enjoyed by most adults. The poliomyelitis complement-fixing antibody, on the contrary, is more transient; it lasts only a year or two after infection and then disappears. The age specific prevalences for complement-fixing antibodies indicate therefore the period of life in which *active* infection or reinfection is going on. In North Africa it is concentrated to a short period in childhood, in spite of the fact that both children and adults must be continuously exposed to the virus there. In the United States, as exemplified by a population in Charleston, West Virginia, where a study was reported by Walton and Melnick,[5] the complement-fixing antibody surveys indicate that the susceptible period of infection and reinfection is much longer. Individuals living under good economic circumstances, continue to get infected or reinfected through young adult life or at least up to the age of 35. As such, poliomyelitis in adults is becoming a growing problem in the United States. Immunity is therefore achieved in this country slowly, and it is getting slower each year,—that is, in the absence of an artificial immunizing agent. The goal for artificial immunization, therefore, is to produce quickly (during infancy) this same *solid, lasting* immunity without having to pay the price which nature exacts, i.e., the occasional paralytic case, and without having to trust to primitive sanitary conditions to provide early exposure to poliomyelitis viruses.

The most highly theoretical ideal of this artificial immunity, therefore, is a vaccine of remarkable potency, of which one course of inoculations might render the vaccinee solidly immune against any reinfection (paralytic or otherwise) for life. But as this is almost too theoretical for this discussion, one turns to another "ideal vaccine" which might prevent paralysis but not necessarily prevent infection, so that, if and when the vaccinee continues to be exposed, he may be prepared for

subsequent infections and may even benefit from them. Thus, when subsequently exposed, he may already possess enough serum antibodies to curtail the spread of virus within the body and particularly within the nervous system; and he may manufacture more antibodies as a result of this reinfection.

On this basis, the idealist's choice of a vaccine might well be a live (attenuated and avirulent) virus which could be employed as an immunizing agent in a natural way, by feeding to infants at the age of six months or before, without presuming that one feeding of such a vaccine would suffice to protect the infant for life. But one feeding might suffice to protect against paralysis for some years. Subsequent natural infections, or refeeding of the vaccine, might then provide the necessary "booster" infections later on. Such a theoretical vaccine might represent three strains administered sequentially, or ideally a single strain having a trivalent group antigen. This virus would be excreted by the vaccinee in his throat or intestinal tract, so that, theoretically again, the intimate contacts of vaccinees might get *their* vaccination gratis, as it were. And it would also be assumed, in fact the whole premise is contingent on the point, that this attenuated "trivalent" strain, or these three strains, would not revert from an avirulent state to a virulent one. All this is quite visionary, but the work of Koprowski and associates[6-8] and Sabin,[9,10] and others, holds out promise, and, although the quest for strains of this type may fall short of the ideal at present, the endeavor is one of infinite importance and should be fruitful.

As to a more contemporary and timely aspect of the subject, namely the idea of a *killed* (formalinized), trivalent virus vaccine to be given parenterally, such as the Salk vaccine, the properties of this vaccine[11,12] have been extensively described in medical literature, as has its capacity to immunize in 1954 and 1955.[13,14] It goes without saying that such a vaccine should not contain *infective* virus, nor any extraneous matter in amounts large enough to sensitize the vaccinee and thus produce undesirable side reactions as a result of one or multiple courses of injection. Obviously it should have antigenic potency. As an added factor of safety, the substitution of avirulent, attenuated strains for virulent strains within such a killed (formalinized) vaccine might seem to be a valuable step, provided such strains are shown to have adequate immunogenic potency.[15]

Another point of interest which has not been thoroughly studied as

yet, is the degree to which a killed (formalinized) vaccine can give rise to complement-fixing antibodies in the vaccinee as a measure of its immunizing capacity. Apparently it gives less than does a natural infection.

As to the timing of inoculations no alterations in the proposed schedule used at present are suggested, but as to the route of inoculation, something may be said in favor of the *intradermal route*, as used in Denmark in 1955.[16] This latter is based on the idea that it would seem to be less of a traumatic procedure than the intramuscular. Time and observations will answer these questions.

In other words, the current ideal proposed here is that the vaccinee may be given enough immunity, which perhaps can be measured in the form of serum neutralizing antibody, to curtail the spread of virus within the body at the time of each infection (whether apparent or inapparent) and that subsequent single or repeated alimentary infections should again provide the necessary boosters to keep this immunity in constant repair. These subsequent infections could either be *natural*, or conceivably *artificial*, the latter to be given in the form of a live attenuated virus vaccine when and if such a live attenuated vaccine became available.

So we come to the consideration that it may not be a question of deciding between either a dead or a live vaccine against poliomyelitis, but possibly accepting a combination of both. The last suggestion, theoretical though it may sound, would seem to represent a good ideal if paralytic poliomyelitis is to be eliminated to a higher degree and for a longer time than perhaps can be achieved by a killed vaccine alone. And the idea of feeding a live attenuated vaccine to someone who has been given some degree of immunity already, may be more palatable at present than is the idea of feeding attenuated virus to a non-immune. The outlook is hopeful but obviously, the answers will not be found in a day.

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ARS MEDICA

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THE PROBLEMS OF THE ADMINISTRATION OF POLIOMYELITIS VACCINE*

MORRIS GREENBERG**

IN 1954 New York City participated in the national trials of the Salk poliomyelitis vaccine. This was limited to six health areas where incidence of poliomyelitis had been highest in previous years, and comprised a total of about 40,000 children in the first three grades of public and parochial schools, half receiving a placebo material.

Following the report of Dr. Francis and associates[1] indicating favorable results in the 1954 test, the Department of Health was prepared to begin vaccination of all children in grades one and two toward the end of April, with vaccine donated by the National Foundation for Infantile Paralysis. The Cutter incident compelled a delay in the program until the end of May and the beginning of June. Only one injection could be given to the children in those grades. Since then, careful data have been collected on reported cases of poliomyelitis and the findings have been communicated to the Poliomyelitis Surveillance Unit of the Public Health Service in Atlanta. How do these data compare with last year's results? You will recall that Dr. Francis found a 72 per cent over all effectiveness of the vaccine in the placebo areas, or about three and one-half times as many cases in the unvaccinated as in the vaccinated (Table I). This was increased by refining the cases, so that if only bulbar cases were considered, where the diagnosis was more certain, the per cent of effectiveness increased. It increased even more when the diagnosis was confirmed by the laboratory. No deaths occurred among the vaccinated, but 15 occurred among the unvaccinated. Nevertheless, there were some unanswered questions. Why was there only a 60 per cent effectiveness in spinal paralytic cases? Why were the results less favorable in the six year olds than in the seven, eight and nine year olds? Why was protection less against type I virus (68 per cent) than against

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TABLE I.*—PARALYTIC CASES AND DEATHS IN CHILDREN AGES 6, 7, 8 IN POLIOMYELITIS FIELD TRIALS U. S. 1954

	Paralytic Cases			
1. Placebo Areas Children receiving	*Number*	*Rate per 100,000*	*Reduction*	*Deaths*
Vaccine 200,745	33	16	72	0
Placebo 201,229	115	57		4
2. Observed Areas Children receiving				
Vaccine 221,998	38	17	62	0**
None 725,173	330	46		11

* Data from report by Dr. Francis and associates, ref. 1.
**One child developed polio after 2nd injection and after tonsillectomy.

type III (80 per cent) and against type II (100 per cent)?

The results this year are only tentative, since the year is not complete. However, careful data have been kept in the city. As of October 28th there had occurred nine paralytic cases with onsets after June 1st among the 166,000 children in grades one and two that received one injection of vaccine and 19 paralytic cases among the 87,000 children in those grades that did not receive it. The rates were 5.4 and 21.8 per 100,000 respectively, more than four times as many paralytic cases among the unvaccinated as among the vaccinated. In the rest of New York State, where children in ages six to ten years received one injection of vaccine this year, there occurred 14 paralytic cases among the 351,000 vaccinated as compared with 59 paralytic cases among the 282,000 unvaccinated, with respective rates of 4.0 and 20.9 per 100,000, or about five times as high a rate in the latter as in the former. These rates indicate an 80 per cent effectiveness. Tentative reports have been received by the Poliomyelitis Surveillance Unit from a number of states and they indicate generally a 75 per cent effectiveness of the vaccine. It is interesting to note that the New York State figures indicate as much protection from one injection this year as from three injections last year.

Another comparison that has been made by the Poliomyelitis Surveillance Unit is that of the per cent of paralytic cases in different age groups in 1955 as compared with 1952. In most states the five to nine year age group made up a larger percentage of the total amount of

TABLE II.—PARALYTIC CASES OF POLIOMYELITIS BY SPECIFIED AGE GROUPS, NEW YORK CITY 1951-1953 AND 1955 (JUNE 1-OCT. 21)

Age	Paralytic Cases 1951-1953 Number	1951-1953 Per cent	1955 (6/1-10/21) Number	1955 (6/1-10/21) Per cent
0-4	348	27.8	126	35.2
6, 7	169	13.5	29	8.1
5, 8, 9	206	16.4	56	15.6
10-14	214	17.0	54	15.1
15+	319	25.4	93	26.0
Total	1,256	100.0	358	100.0

poliomyelitis in 1952 than in 1955. In this city I have compared 1955 with the three years, 1951-1953. I have further divided the five to nine year age group into the six and seven year olds, most of whom were vaccinated and the five, eight and nine year olds, hardly any of whom received vaccine. You will note that the former group is the only one that shows a marked negative change from the years 1951-1953 (Table II).

When the report by Dr. Francis and associates[1] appeared in April, it was felt that vaccine might be in short supply. The question arose whether a system of priorities for administration of the vaccine should not be recommended. Data were gathered from previous experience in the city. These indicated that the case incidence of poliomyelitis, total as well as paralytic, and the total number of deaths were higher in the five to nine year age group than in any other conventional age group. It was followed by the 0-4, 10-14 and 15-19 year age groups. These facts were presented to the Department's scientific advisory committee, and on its recommendation, the priorities mentioned were established. In the second priority children under one year of age were omitted, since they make up only about 1½ per cent of the total cases. A fifth priority—pregnant women—was included. The rate in this group is 60 per cent higher than in non-pregnant women of the same ages,[2] but is nevertheless still below that of the 15-19 year age group.

One of the questions asked by physicians is what reactions may one expect from injections. Both in 1954 and this year parents were requested to notify the Department of any untoward reaction that

occurred after the injections, and were told that a physician would be sent to examine the child. Some parents took this advice literally, because in one instance the Department physician who visited the child found that it had a fractured leg and in another instance a sprained shoulder. There were 444 calls received and in only 20 instances was there found a general reaction possibly related to the injection—fever of a few hours' duration. About 40 children had mild local reactions. In general, the reactions were less marked than those following the use of pertussis vaccine.

Another question asked is—what are the contraindications to giving the vaccine? I should say they are no different than the contraindications to any other type of immunizing injections. Still another question raised is whether polio vaccine may be given concurrently with other immunizing injections. I don't know of any theoretical objections. Immunity is a specific reaction. Each antigen calls forth a specific antibody. We are all aware that combining diphtheria toxoid with tetanus toxoid and pertussis vaccine does not diminish the sensitizing strength of any of the three antigens in the mixture. I don't know of any theoretical objection to giving polio vaccine at the same time. I have been asked by physicians whether polio vaccine may be given before a tonsillectomy. I can see no reason why it should not, although I question the indications for most tonsillectomies.

Many physicians have been concerned about giving the vaccine to children with definite allergies, since small amounts of penicillin and streptomycin are added to the culture flasks to inhibit bacterial growth. Our own experience is similar to that of the rest of the country. There have been no serious allergic reactions. One investigator[3] skin-tested a group of individuals sensitive to various inhalants and gave them injections of the vaccine, with no untoward results. He also tested two individuals who were highly sensitive to penicillin, with the vaccine and later gave them injections of the vaccine with completely negative results regarding allergic sensitivity.

The question of Rh sensitivity has been raised, since the vaccine is grown in monkey kidney culture flasks. Wiener has stated that Rh antigens in the monkey are attached to the red cells only. These are completely washed out, when the kidney is used. Francis reports that Rh negative children who were injected with the vaccine were tested for Rh and Hr antibodies.[1] None were found. A group from the Child-

ren's Hospital in Philadelphia tested for the presence of Rh antigens by sensitizing individuals to the Rh factor and, when the antibodies had fallen, injecting them with polio vaccine. No booster effect resulted.[4] It is apparent that there need be no fear of Rh sensitization.

A more serious fear has been expressed—that, since the culture in which virus is grown contains monkey kidney, the possibility of kidney damage may result from sensitization to kidney tissue. The report by Dr. Francis and associates[1] states that Mayer searched for complement fixing antibodies against monkey kidney in 100 persons who had received multiple doses of vaccine but found none. Neva studied 15 vaccinated children intensively, using various tests, including daily Addis counts, but found no evidence of kidney damage.

A good deal has been said about the provocative effect of the injection. Several years ago some English investigators showed that if a child receives an immunizing injection with pertussis vaccine or diphtheria toxoid and is exposed to poliomyelitis within a few weeks he is more apt to be paralyzed in the injected limb than if he had not received the injection.[5] Several investigators in this country confirmed the findings.[6] Bodian[7] has performed the experiments in monkeys with similar results. The question arises, therefore, should primary vaccination against poliomyelitis be done during the poliomyelitis season and particularly during an epidemic? The national advisory committee could not agree on the answer so the Surgeon General told health officers and private physicians to make up their own minds about it. The proponents of injections say that more children will be saved from paralysis by the vaccination than will have the disease provoked by the injection. In New York City, primary injections have not been advised during the summer.

What is the present situation with regard to availability of vaccine? The National Foundation for Infantile Paralysis has supplied vaccine to children in grades one and two and to those who were in last year's (1954) trial areas, about 13,000,000 cc. Each child received two doses. In New York City about 187,000 children received this vaccine. The Congress has appropriated some 30 million dollars for the purchase of vaccine for persons under 20 years of age and for pregnant women of any age. New York State's share is $1,700,000 worth. New York City is entitled to 46 per cent of that. Under the law each state can decide on the distribution provided the vaccine is limited to persons

under 20 years and pregnant women. The advisory committee to the State Health Commissioner has recommended the limitation of the use of this vaccine to children in the five to nine year age group—kindergarten through fifth grade. The manner of distribution varies in different states. Some have distributed all their allotted vaccine to private physicians. Others have allocated all of it to public health agencies. Some, New York State included, have allocated part to public health agencies and part to private physicians. In New York City, as in most large communities in the state, the distribution is by the Department of Health in school clinics. Apart from the federal program, there exists a voluntary allocation program. The State Department of Health is the agency which decides on the distribution of all vaccine entering the state. In New York, the state advisory committee has recommended that until the five to nine year program is completed all vaccine entering the state, irrespective of source, should be allotted 80 per cent to public health agencies and 20 per cent to private physicians through the drug trade. As soon as the five to nine year group is immunized, the amount allotted for sale to physicians will go up to 30 per cent. On October 21st, at the last meeting of the advisory committee, 53,000 cc. of vaccine had been allotted to the drug trade for sale to physicians.

In New York City the program for vaccinating the five to nine year age group begins in November. Two injections will be given to each child in the kindergarten through fifth grade who has not previously been injected and who presents a parental request form. The program will begin in Queens and will continue in Manhattan, Brooklyn and Bronx, allowing a month for each borough. Richmond will develop its vaccination program concurrently. This program is predicated on the receipt of sufficient vaccine. Next year it is planned to make vaccination against poliomyelitis part of the Department's regular immunization program. As with diphtheria, tetanus and pertussis immunization, and vaccination against smallpox, parents will be urged to get poliomyelitis vaccination for their children from their own doctors. Those who cannot or will not, will be able to get it from Department physicians. The experience in the city has been that 50 per cent of children go to their own doctors.

What are the prospects of obtaining vaccine? All I can tell you is what I read in the newspapers. On October 24th, the New York

Times stated that government officials have been clearing about 5,000,000 cc. of vaccine a month, but none would predict how much vaccine would be on the market by the end of the year. Some have estimated that there would be enough vaccine by 1956 to provide 2 shots for the 16,000,000 children in the five to nine year age group. In New York City we have about half a million such children.

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NEW YORK PATHOLOGICAL SOCIETY

Meeting of December 1, 1955 at The New York Academy of Medicine*

SOME ASPECTS OF THE PATHOLOGY OF COLLAGEN DISEASES**

LEON SOKOLOFF

ORIGINALLY conceived, the term "collagen diseases" connoted a group of maladies in which the characteristic pathologic processes involved widespread alteration of the collagenous connective tissues, and more particularly of the intercellular components of those tissues. It has been stated repeatedly by Klemperer[1] that the demonstration of certain morphological similarities among the several entities did not in any manner imply that there were morphological identities, common pathogenetic mechanisms or a common etiological background. The value of the concept of collagen diseases lay in the possibility that by focussing attention on the previously generally neglected structure and function of the collagenous connective tissues, a clearer understanding of the pathogenesis of the individual diseases might be obtained.

For the purposes of the present discussion, it is assumed that the group of collagen diseases includes rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, scleroderma and polyarteritis nodosa. There is widespread belief that the various collagen diseases are closely related to each other in their fundamental pathological processes; that they individually have inconstant and protean manifestations and present, for this reason, a spectrum of lesions in which one disease merges imperceptibly with the others; that the collagen diseases each share a vascular lesion that is fundamentally related to polyarteritis nodosa; and that they represent some manifestation of hypersensitivity.

In the absence of more definitive tests, the evidences that the collagen

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diseases do in fact represent a closely related group are circumstantial. They are of several sorts: 1) The demonstration that there are striking pathological similarities among the several entities; 2) the demonstration that these disorders may coexist or apparently undergo transition from one into the other; 3) the clinical demonstration that allergic types of vascular and mesenchymal disease have some similarities to some of the collagen diseases; 4) the experimental demonstration that some of the manifestations of collagen diseases may be reproduced by anaphylactic hypersensitivity. Two lesions of scleroderma that we have observed recently will serve as a basis for considering the problem of pathological similarities and the inferences that may be drawn from them with respect to the coexistence of several collagen diseases and a common vascular abnormality.

Synovitis Encountered in Scleroderma

In scleroderma, disability of the joints is often an outstanding feature. In a large proportion of patients, pain and, more often, stiffness of the joints dominate the clinical picture. In a large proportion of cases, a diagnosis of rheumatoid arthritis is made prior to the recognition of scleroderma. Nevertheless, the articular changes are usually interpreted to be the result of the cutaneous sclerosis. This leads to mechanical restriction of the joint motion and to a trophic destruction of the bone and joint. Although passing mention is made of fibrinoid change in the synovial tissues in scleroderma by Bennett and Dallenbach[2] and by Kulka, Bocking, Ropes and Bauer,[3] the occurrence of synovitis has apparently not been treated systematically previously. We have had the opportunity to examine synovial tissue of the knee from six patients with scleroderma. In four of these, well-developed inflammatory changes were present.

CASE 1: This patient was a 44 year old woman who died nine months following the onset of symptoms referable to scleroderma. Initially her complaints were pain and stiffness of her fingers, shoulders, knees and ankles. These were followed shortly by increasing tightening of the skin of the face, extremities and trunk. There was no improvement from a brief course of treatment with cortisone. When she was admitted to the Clinical Center of the National Institutes of Health, physical examination revealed marked induration and thickening of the skin. It glistened excessively. Numerous venous telangiectases were present. Biopsy of the skin of the forearm and several other sites revealed a pattern of dermal sclerosis quite characteristic of scleroderma. During the three months that followed, symptoms of systemic involvement, including dysphagia, progressed. During this period, the patient received no

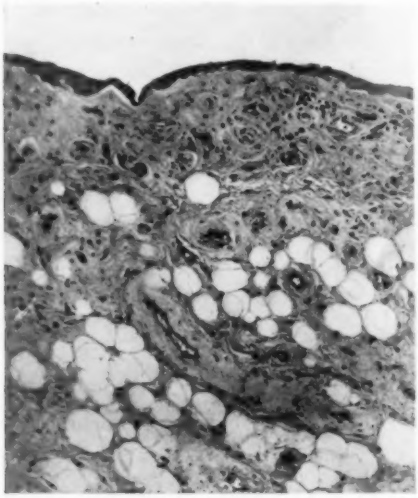

Figure 1

steroid medication. On several occasions, Lupus Cell tests were performed and were negative. The sheep red cell agglutination test was negative. Synovial membrane was obtained from the knee by closed biopsy and then at necropsy. The sections disclosed at first an acute and, later, a chronic organizing fibrinous synovitis (Fig. 1). The surface of the membrane was denuded of lining cells and covered by a compact layer of fibrin. Subjacent to this, the synovial adipose tissue was becoming fibrotic. There was some minor infiltration of plasma and mononuclear cells.

CASE 2: The second patient was a 50 year old woman who had had Raynaud's phenomenon for four years. Two years after the onset of Raynaud's phenomenon, aching developed in the hips, hands and knees and stiffness in the fingers. When she was admitted to the Clinical Center, the skin was found to be thickened and excessively pigmented. L.E. Cell preparations were negative on two occasions as were four sheep red cell agglutination tests. X-ray examination of the hands revealed considerable narrowing of the interphalangeal joint spaces and calcification of the soft tissue of the index finger. Dermal fibrosis, compatible with scleroderma, was found on biopsy. Open biopsy of the knee was carried out under local anesthesia. Excessive quantities of turbid fluid were present in the joint cavity, and the surface appeared opaque and thickened. Sections revealed a moderately severe chronic inflammatory reaction in the synovial membrane. There were numerous infiltrates of chronic inflammatory cells, aggregated principally about the blood vessels. In many areas, the surface was capped by compact fibrinous exudate in an advanced state of organization.

CASE 3: This patient was a 54 year old man who had pain, swelling and stiffness of many joints for four years. Two years after the arthritis appeared, there was an onset of Raynaud's phenomenon and scleroderma. Esophageal involvement was found by roentgenographic study. L.E. Cell preparations were negative. The sheep cell

agglutinin titer was 32 on one occasion, and negative two other times. Biopsy of the skin confirmed the diagnosis of scleroderma. Open biopsy of the knee revealed chronic synovitis of moderate proportion. It was characterized variously by focal infiltration of lymphocytes in the superficial portions of the synovial membrane, by a degree of fibrosis, and focal ulceration of the surface with fibrinous exudation.

CASE 4: This patient was a 35 year old woman who had manifestations of arthritis for six years, and was treated at different times with gold, corticotropin and cortisone. At another institution an L.E. Cell preparation was reported positive on one occasion. Subsequent to that time, repeated L.E. Cell preparations were made at the Clinical Center and were consistently negative. On one of two occasions, the sheep red cell agglutinin titer was elevated to 64. The physical appearance and histological character of the skin changes were pathognomonic of scleroderma. Open biopsy of the knee joint revealed mild but definite chronic inflammatory changes similar to those already described.

In addition to these patients, we have seen mild fibrinous synovitis of the knee at necropsy in a patient at another hospital in whom arthritis of the knee was not suspected clinically.

It appears, then, that chronic synovitis is an important manifestation of scleroderma. This observation provides another point of similarity among scleroderma, disseminated lupus erythematosus, rheumatoid arthritis, and, up to a point, rheumatic fever. Are we warranted in concluding that the pathogenesis of the synovitis is the same in each of the disorders or that we are dealing with coexisting rheumatoid arthritis or lupus erythematosus? It is to be noted that the synovial lesions in these four cases are morphologically non-specific; they are of the type found in rheumatoid arthritis, albeit milder. The serological tests do not give reason to believe that they are in fact the same. The Lupus Cell tests were consistently negative at the Clinical Center. The sheep cell agglutination test was usually negative although two individual determinations were within the low positive range. Insofar as the tissue reaction is morphologically non-specific, the proof of the identity with the other collagen diseases would have to rest on some other test as yet undiscovered.

Renal Lesions in Scleroderma

The renal lesions of scleroderma have been receiving increased attention in recent years. This reflects, in part, a clinical concern with an alleged harmful effect of steroid therapy. A number of reports have dealt with the precipitation of a rapidly progressive course of malignant hypertension by the administration of corticotropin and cortisone in scleroderma.[4, 5] The steroids have been reported to produce a similar

syndrome or polyarteritis nodosa in other collagen diseases as well.[6-9] We have had the privilege of studying renal lesions from five patients with scleroderma. These cases will be reported shortly by Rodnan, Schreiner and Black. They are being presented to illustrate the fact that, although there are certain striking similarities to lesions in other collagen diseases, there is reason to believe that a very different pathogenic mechanism is involved in scleroderma than those suspected in the other conditions.

CASE 5: The patient was a 27 year old woman who had scleroderma for two years before she died. She was treated with cortisone for a two month period 18 months before she died, and received no steroid medication subsequently. The L.E. cell test was negative. Her blood pressure was normal and she had no evidence of renal insufficiency until two weeks before she died. At that time, the onset of malignant hypertension was heralded by convulsive seizures. The blood pressure was 170/130 and rose to 240/150. The urine contained large amounts of albumin. The blood urea nitrogen concentration rose to 102 mg. per 100 cc. before she died. At necropsy, the kidneys were not contracted but contained numerous small areas of recent infarction. Microscopically, vascular lesions of several sorts were seen: in the arcuate and interlobular arteries, one could distinguish old and recent pathologic changes. The older lesions were characterized by a prominent thickening of the intima by laminated fibrous tissue of loose texture. In many instances, the intimal sclerosis had progressed to the point that the lumen was largely obliterated. In the more recent lesions, a compact, homogeneous material having the tinctorial appearance of fibrin was deposited apparently upon and within the intima. The deeper portions of the vessel wall were necrotic in some areas, but infiltration by inflammatory cells was conspicuous by its paucity. The afferent arterioles and a proportion of the capillaries in the glomerular tufts were involved by recent fibrinoid necrosis like that seen in the arteries. The walls were necrotic and fibrin-like material with enmeshed red cells and other hematic elements adhered to them.

CASE 6: The second patient had not been treated with steroid preparations but died with rapidly progressive renal insufficiency and hypertension. There were multiple small cortical infarcts in the kidneys. Changes indistinguishable from those of the preceding patient, were present in the vessels. The walls of the afferent arterioles and some of the capillaries were necrotic. A fibrin-like coagulum that enmeshed other elements of the blood adhered to them.

Similar lesions were present in the two other patients with rapidly developing renal insufficiency and hypertension.

The lady first presented (Case 1), who had arthritis and died nine months following onset of scleroderma, also had renal lesions. She had not received steroid preparations during the three months prior to death, during which period there was a rapidly progressive development of systemic disease, except that cortisone therapy was started again as a matter of desperation two days before the patient died, while she was in extremis. Hypertension and renal insufficiency were not present.

Nevertheless at necropsy, acute vascular lesions like those already seen were present in the interlobular arteries, glomerular capillaries, and in numerous minute splanchnic vessels.

The lesions described here are like those reported previously by others.[10, 11] They involve fundamentally changes in the small blood vessels and secondary, focal parenchymal reactions. The vascular lesions are of two sorts: 1) a proliferative sclerosis of the arcuate and interlobular arteries and 2) an acute "fibrinoid" necrosis of afferent arterioles, glomerular capillaries and, to a lesser extent, of the small arteries. Inasmuch as the inclusion of scleroderma among the collagen diseases rested originally upon the observation of fibrinoid necrosis in the blood vessels, these vascular lesions provide a particularly interesting area for evaluating the unitary concept of the collagen diseases.

In each instance, a cellular exudate was absent or minimal in the vascular lesions. They differed in this respect from the typical lesions of polyarteritis nodosa. Unlike lupus erythematosus, they did not lead to a nephritic reaction; hematoxylin bodies were absent; the fibrinoid material was more heterogeneous and differed, perhaps, in some respects from those of lupus. They appeared to be indistinguishable from those of malignant hypertension (as distinguished from nephrosclerosis) on one hand, and quite like those reported by Lewis[12] in the digital vessels in Raynaud's phenomenon associated with scleroderma. It is noted that the renal vascular lesions in four of the five present cases of scleroderma were associated with malignant hypertension, a state in which the vessels are also in a spastic condition. It would not appear unreasonable to consider the likelihood that the vascular changes in the kidney of scleroderma are akin to those found in the peripheral vessels; that, so to speak, we are dealing with Raynaud's phenomenon in the kidney.

This hypothesis suggests that there is an abnormal state of vasoconstriction and dilatation in various portions of the vascular bed in scleroderma; and that the fibrinoid necrosis may well be secondary to the abnormal function of the vessel. It is noted in this regard, that a pattern of fibrinoid necrosis of arteries has been produced experimentally in animals by administration of adrenalin.[13] In view of the fact that hypertension had not made its appearance in one of the patients with the renal lesion, hypertension per se would not appear to be a cause of the necrosis but the result of the abnormal vasomotor state that also induces the necrosis. At the present time, there is little reason to impli-

cate a mechanism of hypersensitivity in the development of Raynaud's phenomenon or malignant hypertension.

Since it is proper and necessary that we speculate about the meaning of these observations, I would like to venture some suggestions:

1. Among the collagen diseases, there are striking clinical and pathological similarities in several respects in addition to those that can be interpreted as disturbances of the interstitial portions of the connective tissues. In each there is conspicuous inflammatory reaction in the joints, as well as involvement of portions of the tegumentary system, collagenous tissues of the heart and in the blood vessels and in the striated muscle. In each, these changes are inconstant in character and severity. Many of the changes are lacking in diagnostic specificity. In each, there appears to exist a localized or benign lesion that may undergo rapid systemic progression.

2. The wide distribution of the lesions suggests that they are in some manner mediated by the circulatory system. One thinks of certain similarities of the collagen diseases, say, to those of subacute bacterial endocarditis; and wonders whether some noxae are being disseminated by the blood stream. In the case of systemic lupus erythematosus, evidence has been presented that degraded nucleoprotein is such an agent. In scleroderma, a substance or substances having vasomotor properties may conceivably be involved. Hypothetical circulating antigens would fit into this category of noxae; and, possibly, in the case of rheumatoid arthritis, serum factors responsible for the several diagnostic tests currently being employed.

3. Whether the collagen diseases considered here coexist with any special frequency is a matter of special difficulty, because it involves comparison of matters that largely lack morphological or other diagnostic definition and ultimately defies statistical proof.[14] It is our impression that rheumatoid arthritis and disseminated lupus erythematosus do coexist with some special frequency, and that polyarteritis nodosa also is more common in these collagen diseases than chance would dictate. It may be that polyarteritis nodosa is not to be thought of as a disease per se but an extreme form of segmental, necrotizing arteritis of diverse origins. One can conceive of an exaggerated vascular lesion of scleroderma appearing like polyarteritis nodosa, as it did in the case originally reported by Masugi and Yä.[15]

4. Finally, a word about the role of steroid preparations in precipi-

tating vascular crises in scleroderma and other collagen diseases. It is to be noted that in the cases of scleroderma presented, the vascular lesions had developed in the absence of recent steroid therapy. There can be no question that vascular lesions, including polyarteritis nodosa, do occur in appreciable numbers of patients with rheumatic fever, rheumatoid arthritis and disseminated lupus erythematosus in the absence of steroid therapy. It cannot be denied that steroid and other therapeutic agents may conceivably favor the development of polyarteritis, but this requires more substantial evidence than is available at present.

In conclusion, the observations and speculations about the collagen diseases are substantially in agreement with the view that the entities with which we are dealing have many clinical and pathological similarities, but that we have little compelling evidence at the present time that they share a common single, major pathogenetic mechanism such as hypersensitivity.[1]

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NEW YORK PATHOLOGICAL SOCIETY

ABSTRACT OF PAPER AND DISCUSSION

Some of the Clinical Aspects of Collagen Disease Including Treatment with and without Steroids

LOUIS J. SOFFER

The Mount Sinai Hospital, New York

This presentation deals with 55 patients with acute disseminated lupus erythematosus who were treated with corticotropin or adrenal steroids or their analogues over the course of the past five years. The series included 46 females and nine males, ranging in age from six to 70 years. The patients had evidence of the disease for periods varying from four and a half weeks to 15 years before treatment with these hormonal agents was instituted. Thirty-eight of the 55 patients are alive and 17 have died. Thirteen of the 17 who died, died as a result of progressive renal failure, one succumbed to status epilepticus, one to a disseminated fungus infection, one committed suicide, and one died as a result of inadequate therapy; this last occurred in the early days of treatment, when the amount of hormone available was limited.

Of the 38 living patients, 13 are in a state of remission during which they have received no form of therapy for periods ranging from two to 30 months. The longest period of continuous therapy to date is somewhat over 60 months.

The agents employed include corticotropin, zinc corticotropin, cortisone, hydrocortisone, meticorten, meticortelone, and, in one instance, alpha-9-fluorohydrocortisone. The results with all of these agents in the absence of renal disease were satisfactory, but the dosage of the various agents varied appreciably. In general, the amount of meticorten and meticortelone required to induce and maintain a remission was approximately one-fourth to one-fifth that of cortisone or Compound F. Zinc corticotropin was as effective as the usual intravenously administered corticotropin in equal dosage. Alpha-9-fluorohydrocortisone was a very effective agent in inducing remissions in a small dosage, but tended to cause considerable salt and water retention and, therefore, was deemed unsuitable for prolonged use.

Side effects have occurred with approximately equal frequency with all the agents employed, with the exception of alpha-9-fluorohydrocortisone; this was used in only one case. Some of the side effects could be minimized by careful restriction of salt and fluid intake.

The adrenal steroids and corticotropin play a significant role in the control and management of almost all of the clinical manifestations of disseminated lupus erythematosus, with the exception of the renal damage, which is found to be progressive and unresponsive to steroid therapy.

DISCUSSION

PAUL KLEMPERER: A few days ago I received a letter from Dr. Uehlinger, Professor of Pathology at the University of Zürich, in which he wrote me that he had been lecturing on the collagen diseases, and he added that the concept of these diseases is being clarified more and more. Of course I was pleased with this statement from one

of the Continental authorities, but I am afraid I cannot quite share the optimism of Dr. Uehlinger. The longer one is concerned with the collagen diseases, the more one realizes that the fundamental problem of pathogenesis is far from being clear.

What are the approaches we can use in order to clarify the concept of "collagen diseases"? When Pollack, Baehr and I proposed the term in 1942[1] we stated unequivocally that our main purpose was to call the attention of medical investigators to a group of diseases which are characterized by systemic involvement of the connective tissue, specifically of its intercellular components, and we closed our paper with the hope that physics and chemistry would investigate the collagenous tissues as a colloidal system. We thought that such basic studies might clarify the biology of the connective tissue in the normal human and mammalian body, and were hoping that from such investigations we might become informed about the factors which control the plasticity of the intercellular substances and thus gain insight into the morbid process which underlies their alteration in disease. It was fortunate that Duran-Reynals[2] had actually become interested in the connective tissue problem when he discovered the spreading factor. Meyer[3] likewise had started his investigation of hyaluronic acid by examination of the corpus vitreum and subsequently became aware of the accumulation of this mucopolysaccharide within the connective tissue. This started the chemical approach towards the analysis of the structure of the ground substance. Later the electronmicroscope was applied in the study of the normal collagen fiber. I was hopeful at that time that these advances would contribute to the explanation of the morbid factors influencing the intercellular substances in disease. I am sure that the disclosures supplied by basic science regarding the normal connective tissue are of great importance, but so far we have not been able to bridge the gap between them and our problem, which still is full of the complexities characteristic of problems in medicine. I think that physicians engaged in the observation of the living or dead patient must make their independent contributions, although we must utilize the facts supplied by basic sciences. I cannot share the fear of Dr. Mirsky[4] who asked at the second Josiah Macy Conference on Connective Tissue whether it is not dangerous to use a term like "collagen diseases" because we know so little about what we are talking of. Indeed we do not know much about what we are talking of, and that makes it doubly important that what we are talking about is sharply defined. Delaunay[5] wrote that the term "collagen diseases" takes us back 200 years to the days of Molière's physicians. I believe Delaunay is right if one uses the term in a diagnostic sense. This was not the aim of our proposal. It does not circumscribe in any way a morbid entity. It was proposed as a heuristic idea which might help in the understanding of several obscure pathologic entities which have as a common denominator a complex alteration of the connective tissue. I believe the aim is to decipher this alteration in order to better understand the nature of the separate maladies. In fact, I like to express the hope that if we ever will comprehend the factors which control the normal and abnormal states of the connective tissue, the term "collagen diseases" will have served its purpose and should disappear. But not only basic sciences and experiments will advance our knowledge of the connective tissue, but, I believe, investigations of the morbid states will and must contribute in the present impasse. We should ask, therefore, what anatomic pathology may contribute to an understanding of these diseases and what clinical research. We have to ask ourselves what are the morphologic key manifestations in this group of diseases collectively called "collagen diseases." The microscopic hallmark is fibrinoid alteration of the connective tissue. It occurs in wide distribution and strikingly in the small vessels of the body, as shown by Dr. Sokoloff in his cases of scleroderma. I shall demonstrate photograms of blood vessels from a case of systemic lupus erythematosus and of scleroderma illustrating two types of fibrinoid. It has been assumed in the past that the fibrinoid substances found in these clinically and

anatomically heterogeneous maladies are nevertheless homogeneous in nature and origin. I seriously challenged[8] this assumption because on careful microscopic study one can detect subtle differences in the appearance of the fibrinoid substances in the individual members of the group and these differences are of significance. I think pathologic histology should primarily direct itself toward a clarification of these differences. We must concentrate upon the main problem, and the main problem of anatomic pathology in collagen diseases is to comprehend the nature of fibrinoid. For the identification of the fibrinoid in systemic lupus erythematosus we have histochemical evidence that it contains degradation products of DNA-protein.[7]

I am not a clinician and have no competence to express an opinion on clinical manifestations, but the basic approach which I recommend for the interpretation of the pathologic anatomic lesions should also be valid for the clinician, viz., the concentration of his investigation upon the key manifestations of the collagen diseases. The clinical symptoms are so complex that we cannot hope to get much information from their analysis at the present time. However, there is a laboratory feature which has been emphasized much in the past years, to which Dr. Soffer referred tonight, and this is the abnormality of the blood plasma proteins. These changes are so striking that Ehrich[8] suggested substituting the term dysgammaglobulinemias for collagen diseases. The findings in these blood protein changes, however, are only of low descriptive value. We can use them in making a diagnosis, but if we are seriously concerned with the pathogenetic problem we must search deeper. We must try to identify the nature of the altered blood protein spectra. The results of the investigations of Slater, Ward and Kunkel[9] on the abnormal proteins in multiple myeloma indicate that the globulins in individual cases show definite differences if investigated immunologically. I wonder if the same method applied to the hyperglobulinemia of the collagen diseases might not also reveal interesting facts which could throw light on the pathogenetic problem. This seems particularly appropriate in view of the fact that from anatomic investigations we are led to believe that there is a relationship between blood plasma proteins and the ground substance of the connective tissues.

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SELECTED SUBJECTS OF CURRENT SIGNIFICANCE

MONDAY, OCTOBER 15

Evening Lectures

General Topic: THE PLACE OF HYPOPHYSECTOMY AND ADRENALECTOMY IN THE MANAGEMENT OF NEOPLASTIC AND METABOLIC DISEASES

1. Hypophysectomy in Man
   Rolf Luft, Karolinska Institute, Stockholm, Sweden
2. The Place of Hypophysectomy and Adrenalectomy in the Complications of Diabetes
   Laurance W. Kinsell, Institute for Metabolic Research, Oakland, California
3. The Place of Adrenalectomy in the Management of Severe Hypertension
   Charles C. Wolferth, University of Pennsylvania, Philadelphia, Pa.

TUESDAY, OCTOBER 16

Afternoon Panel Meeting

The Management of Disseminated Neoplastic Diseases

Moderator: David A. Karnofsky

Memorial Center for Cancer and Allied Diseases, New York City

WEDNESDAY, OCTOBER 17

Evening Lectures

General Topic: NEW DRUG THERAPY IN PSYCHIATRY AND HYPERTENSION

1. The Nature of Drugs with Mental Actions and Their Relation to Cerebral Function
   Harry H. Pennes, Eastern Pennsylvania Psychiatric Institute, Philadelphia, Pa.
2. New Drug Therapy in Psychiatry: Clinical Uses and Abuses in Mental Disorders
   Paul H. Hoch, Commissioner of Mental Hygiene, New York State
3. A Clinical Evaluation of Hypotensive Agents
   Irvine H. Page, Cleveland Clinic, Cleveland, Ohio

THURSDAY, OCTOBER 18

Afternoon Clinical-Pathological Conference

Hypertension

Moderator: Alfred Angrist

Albert Einstein College of Medicine, New York City

FRIDAY, OCTOBER 19

Evening Lectures

General Topic: AN EVALUATION OF PRESENT STATUS OF CARDIAC SURGERY

1. Physiological Considerations and Clinical Indications for Cardiac Surgery
   H. B. Burchell, Mayo Clinic, Rochester, Minn.
2. Surgery of Congenital Heart Disease
   Robert E. Gross, Children's Hospital, Boston, Mass.
3. Surgery of Acquired Heart Disease
   Frank Glenn, The New York Hospital-Cornell Medical Center, New York City

MONDAY, OCTOBER 22

Afternoon Panel Meeting

Surgical Management of Cardiovascular Disease

Moderator: Ludwig W. Eichna

New York University-Bellevue Medical Center, New York City

TUESDAY, OCTOBER 23

Evening Lectures

General Topic: THE ADRENAL CORTICAL STEROIDS AND THEIR ANALOGUES

1. Biosynthesis of Adrenal Cortical Hormones
   Gregory Pincus, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass.
2. The Role of the Adrenal Cortical Steroids and Their Analogues in Electrolyte and Fluid Metabolism
   Louis J. Soffer, The Mount Sinai Hospital, New York City
3. Clinical Uses and Hazards of the Adrenal Hormones and Their Analogues in the Management of Rheumatic Diseases
   Joseph J. Bunim, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland

WEDNESDAY, OCTOBER 24

Afternoon Clinical-Pathological Conference

An Endocrine Problem

Moderator: John G. Kidd

The New York Hospital-Cornell Medical Center, New York City

THURSDAY, OCTOBER 25

Evening Lectures

General Topic: POLIOMYELITIS

1. The Nature of Viruses
   Mark H. Adams, New York University-Bellevue Medical Center, New York City
2. Present Status of Attenuated Live Virus Poliomyelitis Vaccine
   Albert B. Sabin, The Children's Hospital Research Foundation, Cincinnati, Ohio
3. Recent Experience and Present Status of Killed Virus Poliomyelitis Vaccine
   Joseph E. Smadel, National Institutes of Health, Bethesda, Maryland

FRIDAY, OCTOBER 26

Afternoon Panel Meeting

Therapy of Infections

Moderator: David E. Rogers

Division of Infectious Diseases, The New York Hospital-Cornell Medical Center, New York City

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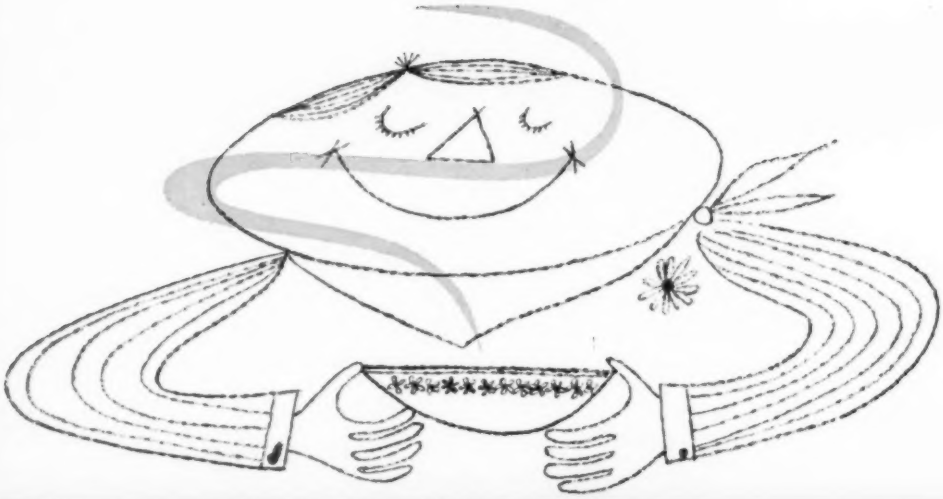

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2. Fluctuating subtotal hearing loss, usually affecting the higher tones, is noted at the same time as vertigo.
3. Tinnitus, usually unilateral, is associated with the deafness and dizziness.

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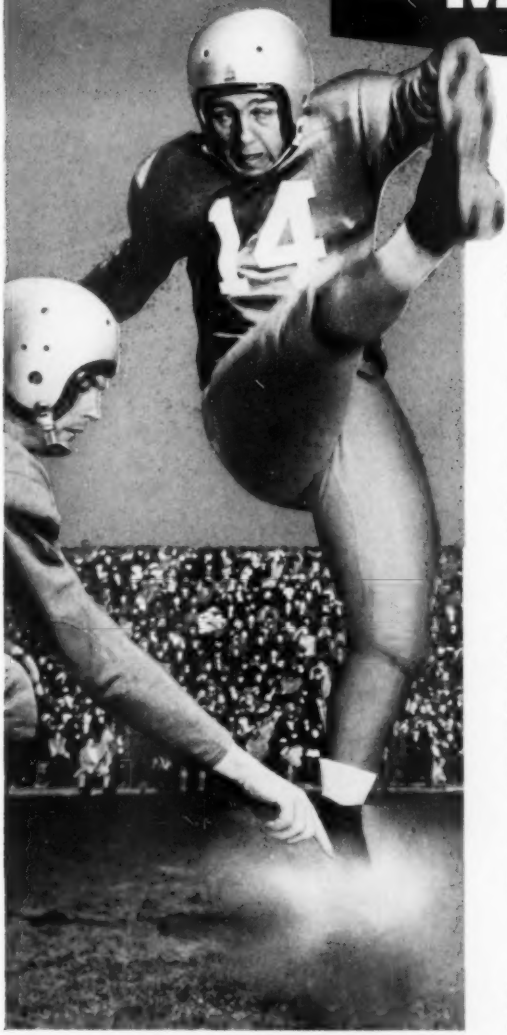

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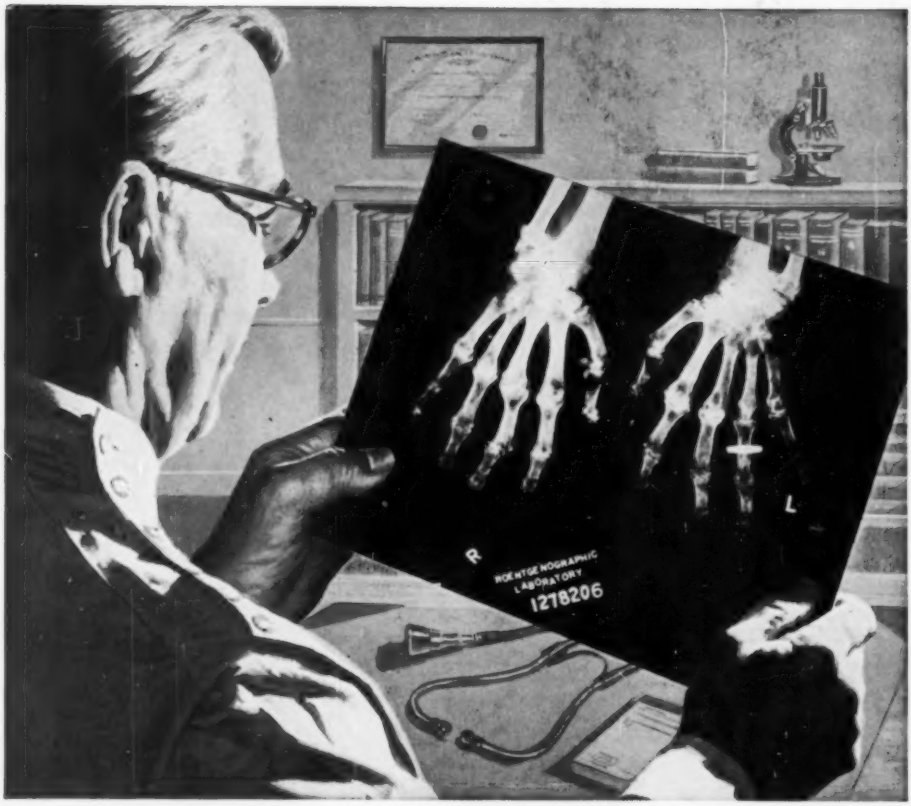

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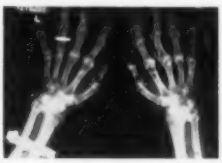

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It's the time of year when people crowd together and sore throats spread. For these mixed bacterial throat infections, TETRAZETS troches provide continuing local therapy. The 3 potent antibiotics in TETRAZETS have a low index of toxicity and sensitization. Each TETRAZETS troche contains zinc bacitracin 50 units, tyrothricin 1 mg., neomycin sulfate 5 mg., and anesthetic benzocaine 5 mg.

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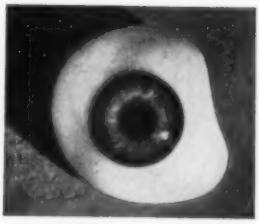

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why not get a nice new one at your Surgical Dealer's.

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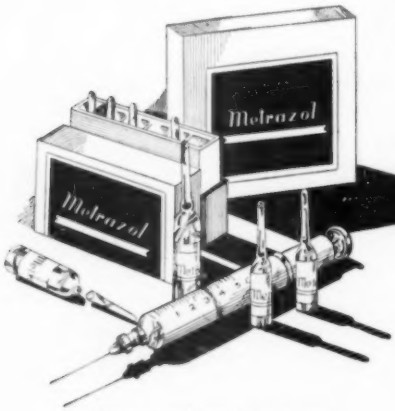

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For Intramuscular Use

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in a Stabilized Aqueous solution

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Reserpoid *(Pure crystalline alkaloid)*

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Each tablet contains:
Reserpine ..... 0.1 mg.
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The elixir contains:
Reserpine ..... 0.25 mg.
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Supplied:
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Elixir in pint bottles

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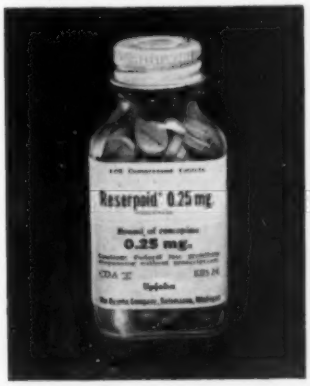

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for prenatal vitamin-mineral protection,

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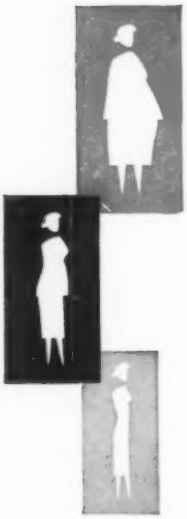

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Contain calcium ... no phosphorus

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Contain both calcium and phosphorus

Both alike in patient acceptance

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Lift the depressed patient up to normal without fear of overstimulation . . .

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Ritalin®

A HAPPY MEDIUM IN PSYCHOMOTOR STIMULATION

• *Boosts the spirits, relieves physical fatigue and mental depression . . . yet has no appreciable effect on blood pressure, pulse rate or appetite.*

Ritalin is a mild, safer central-nervous-system stimulant which gently improves mood, relieves psychogenic fatigue "without let-down or jitters . . ."[1] and counteracts oversedation caused by barbiturates, tranquilizing agents and antihistamines.

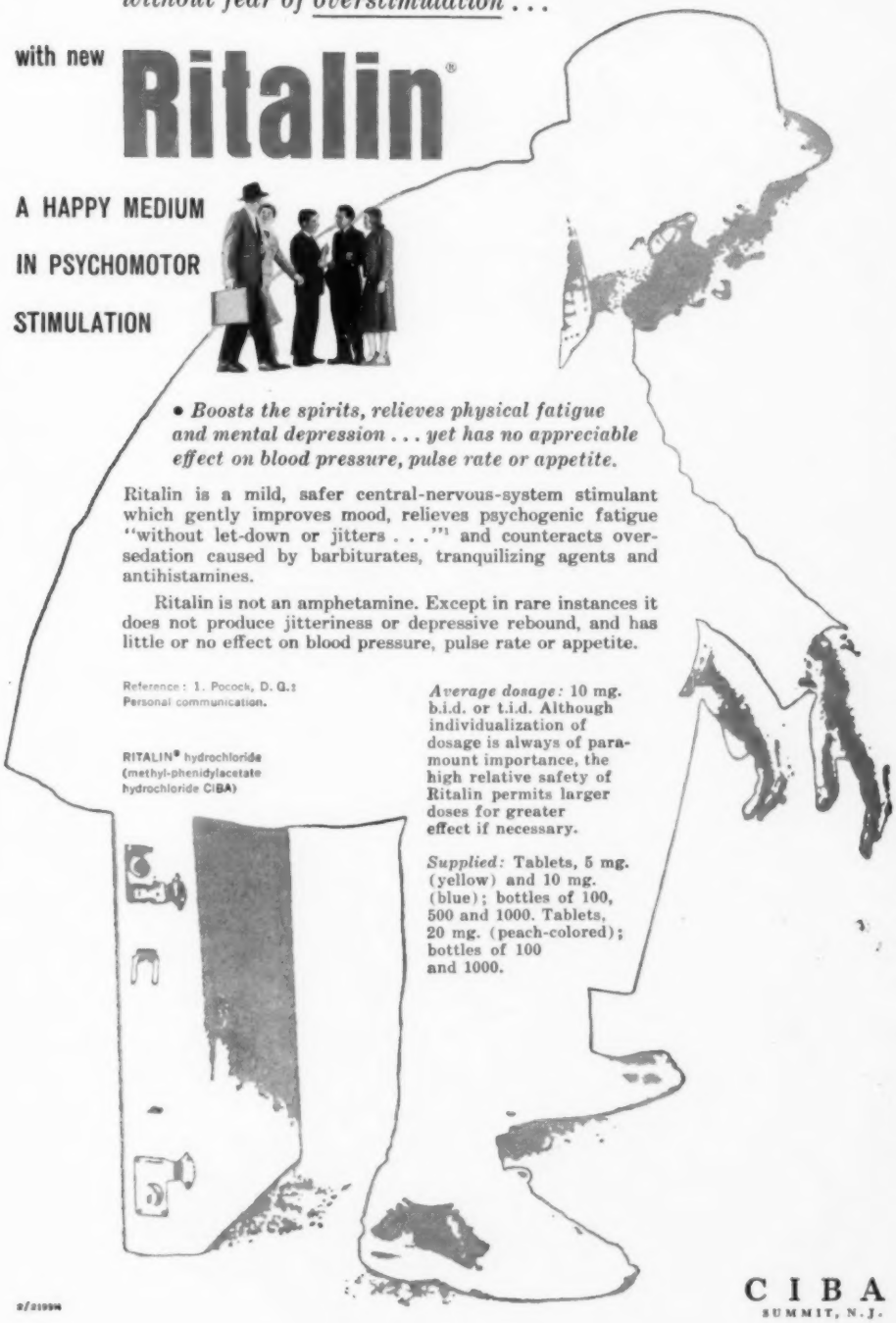
Ritalin is not an amphetamine. Except in rare instances it does not produce jitteriness or depressive rebound, and has little or no effect on blood pressure, pulse rate or appetite.

Reference: 1. Pocock, D. G.: Personal communication.

RITALIN® hydrochloride (methyl-phenidylacetate hydrochloride CIBA)

Average dosage: 10 mg. b.i.d. or t.i.d. Although individualization of dosage is always of paramount importance, the high relative safety of Ritalin permits larger doses for greater effect if necessary.

Supplied: Tablets, 5 mg. (yellow) and 10 mg. (blue); bottles of 100, 500 and 1000. Tablets, 20 mg. (peach-colored); bottles of 100 and 1000.



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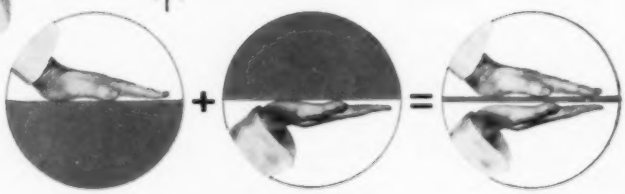
CIBA
SUMMIT, N.J.

STABILIZE

the up and down patient



Serpasil
tranquilizer

Ritalin
psychomotor stimulant

Serpatilin
emotional stabilizer

To induce emotional equilibrium in those who swing from anxiety to depression, Serpatilin combines the relaxing, tranquilizing action of Serpasil with the mild mood-lifting effect of the new cortical stimulant, Ritalin. In recent months, numerous clinical studies have indicated the value of combining these agents for the treatment of various disorders marked by tension, nervousness, anxiety, apathy, irritability and depression. Arnoff,[1] in a study of 51 patients, found the combination of definite value in a variety of complaints, noting no effect on blood pressure or heart rate. Lazarte and Petersen[2] also found Serpatilin effective in counteracting the side effects of reserpine and chlorpromazine. They reported: "The stimulating effect of Ritalin seemed complementary to the action of reserpine . . . in that it brought forth a better quality of increased psychomotor activity."

1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

Serpatilin Tablets, 0.1 mg./10 mg., each containing 0.1 mg. Serpasil® (reserpine CIBA) and 10 mg. Ritalin® hydrochloride (methyl-phenidylacetate hydrochloride CIBA).

Dosage: 1 tablet b.i.d. or t.i.d., adjusted to the individual.

Serpatilin T.M.

(reserpine and methyl-phenidylacetate hydrochloride CIBA)

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MYSTECLIN SUSPENSION

Steclin-Nystatin (Squibb Tetracycline-Nystatin)

Another form of the only broad spectrum antibiotic preparation with added protection against monilial superinfection

PLEASANT TASTING — Mysteclin Suspension is pleasantly fruit-flavored and will appeal to taste-conscious youngsters as well as to adults who prefer liquid medication.

BROADLY EFFECTIVE — Mysteclin Suspension provides well tolerated therapy for the many common infections which respond to tetracycline—and also acts to prevent monilial overgrowth.

READY-TO-TAKE — Mysteclin Suspension requires no reconstitution and can be given by simple teaspoon dosage to patients of all ages.

MYSTECLIN SUSPENSION: a fruit-flavored oil suspension containing the equivalent of 125 mg. Steclin (Squibb Tetracycline) Hydrochloride and 125,000 units Mycostatin (Squibb Nystatin) per 5 cc. teaspoonful. Supplied in two-ounce bottles.

Also available as Capsules (250 mg. Steclin Hydrochloride and 250,000 units Mycostatin) and Half Strength Capsules (125 mg. Steclin Hydrochloride and 125,000 units Mycostatin).

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By Ivan Belknap, Ph.D., Associate Professor of Sociology, University of Texas. The main thesis of the book is that the state mental hospital has become a large, centralized, geographically isolated, and impersonal institution; an institution which is, itself, a major obstacle to the application of modern psychiatric techniques to the treatment of mental illnesses. The study attempts to show the adverse effects of present organization of the state hospital and recommends experimental changes in organization to overcome some of these disadvantages. 265 pages, 6 x 9, 9 illustrations, $5.50. *In Press for October publication.*

Sataloff—Industrial Deafness

By Joseph Sataloff, M.D., Assistant Professor of Otology, Jefferson Medical College; Visiting Professor Audiology and Co-director of Industrial Deafness Course, Colby College; Consultant in Audiology, Veterans Administration; Audiologist to the Children's Hospital, Philadelphia. In this book all phases of industrial deafness are treated in a single volume for use by those who have the responsibility of solving the many problems of industrial deafness and noise. Section one of the book deals with physics of sound, anatomy of the ear, causes of deafness; section two tells how to measure noise; section three tells how to measure hearing and how to organize a conservation-of-hearing program. Approx. 350 pages, 6 x 9, 75 illustrations. *In Press for November publication.*

Graham, Mullen—Rehabilitation Literature 1950-1955

By Earl C. Graham, Librarian, and Marjorie M. Mullen, Assistant Librarian, National Society for Crippled Children and Adults. This all-inclusive review indexes and annotates 5,214 periodical articles, pamphlets and books relating to the medical care, education, employment, welfare and psychology of handicapped children and adults. Here, in one alphabetical listing by subject, are the references published in the six-year period from January, 1950 to December, 1955. The authors bring to the whole rehabilitation field the skill and experiences of the Library of the National Society for Crippled Children and Adults, well known for its bibliographic activities. 573 pages, 7 x 10. *In Press for October publication.*

Grotjahn—Beyond Laughter: A Psychoanalytic Approach to Humor, Wit, and the Comic.

By Martin Grotjahn, M.D., Associate Clinical Professor of Psychiatry, The University of Southern California; Former Director of Research, Institute for Psychoanalytic Medicine of Southern California. Written in an unusually ingratiating style, this is a book in which, as the author says, one can "read about laughter without crying." This is one of the first books since Freud's works on jokes that makes a systematic attempt to describe the psychoanalysis of problems relating to wit, humor, and the funny. The author discusses certain aspects of the analytical interpretation of humor: the development of the sense of the funny in the child; the psychodynamic origin of Comedy, Clowns, Burlesque Queens, and the Circus. 304 pages, 6 x 9, 13 cartoons. *In Press for November publication.*

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By Evelyn S. Stead and Gloria K. Warren, Dietitian, with an introduction by Eugene A. Stead, Jr., M.D., and James V. Warren, M.D. This book will prove helpful to the doctor who wishes to reduce the fat intake of patients with heart disease, vascular disease, or diabetes. The authors provide interesting recipes for palatable dishes which do not carry the stigma of privation common to most diets. The book is written primarily for the use of well persons who wish to control their weight without reducing the amount of food they eat, or who wish to reduce their intake of fat in the belief that this is a reasonable step in the preventive approach to vascular disease. Approx. 225 pages, 5⅝ x 8, illustrated. *In Press for October publication.*

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